TITLE OF THE INVENTION

N-(BENZYL)AMINOALKYLCARBOXYLATES, PHOSPHINATES, PHOSPHONATES AND TETRAZOLES AS EDG RECEPTOR AGONISTS

BACKGROUND OF THE INVENTION

The present invention is related to compounds that are $S1P_1$/Edg1 receptor agonists and thus have immunosuppressive activities by producing lymphocyte sequestration in secondary lymphoid tissues. The invention is also directed to pharmaceutical compositions containing such compounds and methods of treatment or prevention.

Immunosuppressive agents have been shown to be useful in a wide variety of autoimmune and chronic inflammatory diseases, including systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis and other disorders such as Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy, atopic dermatitis and asthma. They have also proved useful as part of chemotherapeutic regimens for the treatment of cancers, lymphomas and leukemias.

Although the underlying pathogenesis of each of these conditions may be quite different, they have in common the appearance of a variety of autoantibodies and/or self-reactive lymphocytes. Such self-reactivity may be due, in part, to a loss of the homeostatic controls under which the normal immune system operates. Similarly, following a bone-marrow or an organ transplantation, the host lymphocytes recognize the foreign tissue antigens and begin to produce both cellular and humoral responses including antibodies, cytokines and cytotoxic lymphocytes which lead to graft rejection.

One end result of an autoimmune or a rejection process is tissue destruction caused by inflammatory cells and the mediators they release. Anti-inflammatory agents such as NSAIDs act principally by blocking the effect or secretion of these mediators but do nothing to modify the immunologic basis of the disease. On the other hand, cytotoxic agents, such as cyclophosphamide, act in such a nonspecific fashion that both the normal and autoimmune responses are shut off. Indeed, patients treated with such nonspecific immunosuppressive agents are as likely to succumb to infection as they are to their autoimmune disease.

Cyclosporin A is a drug used to prevent rejection of transplanted organs. FK-506 is another drug approved for the prevention of transplant organ rejection, and in particular, liver transplantation. Cyclosporin A and FK-506 act by inhibiting the body's immune system from mobilizing its vast arsenal of natural protecting agents to reject the transplant's foreign protein. Cyclosporin A was approved for the treatment of severe psoriasis and has been approved by European regulatory agencies for the treatment of atopic dermatitis.

Though they are effective in delaying or suppressing transplant rejection, Cyclosporin A and FK-506 are known to cause several undesirable side effects including nephrotoxicity, neurotoxicity, and gastrointestinal discomfort. Therefore, an immunosuppressant without these side effects still remains to be developed and would be highly desirable.

The immunosuppressive compound FTY720 is a lymphocyte sequestration agent currently in clinical trials. FTY720 is metabolized in mammals to a compound that is a potent agonist of sphingosine 1-phosphate receptors. Agonism of sphingosine 1-phosphate receptors induces the sequestration of lymphocytes (T-cells and B-cells) in lymph nodes and Peyer's patches without lymphodepletion. Such immunosuppression is desirable to prevent rejection after organ transplantation and in the treatment of autoimmune disorders.

Sphingosine 1-phosphate is a bioactive sphingolipid metabolite that is secreted by hematopoietic cells and stored and released from activated platelets. Yatomi, Y., T. Ohmori, G. Rile, F. Kazama, H. Okamoto, T. Sano, K. Satoh, S. Kume, G. Tigyi, Y. Igarashi, and Y. Ozaki. 2000. *Blood.* 96:3431-8. It acts as an agonist on a family of G protein-coupled receptors to regulate cell proliferation, differentiation, survival, and motility. Fukushima, N., I. Ishii, J.J.A. Contos, J.A. Weiner, and J. Chun. 2001. Lysophospholipid receptors. Annu. Rev. Pharmacol. Toxicol. 41:507-34; Hla, T., M.-J. Lee, N. Ancellin, J.H. Paik, and M.J. Kluk. 2001. Lysophospholipids - Receptor revelations. *Science.* 294:1875-1878; Spiegel, S., and S. Milstien. 2000. Functions of a new family of sphingosine-1-phosphate receptors. *Biochim. Biophys. Acta.* 1484:107-16; Pyne, S., and N. Pyne. 2000. Sphingosine 1-phosphate signalling via the endothelial differentiation gene family of G-protein coupled receptors. *Pharm. & Therapeutics.* 88:115-131. Five sphingosine 1-phosphate receptors have been identified ($S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$, and $S1P_5$, also known as endothelial differentiation genes Edg1, Edg5, Edg3, Edg6, Edg8), that have widespread cellular and tissue distribution and are well conserved in human and

rodent species (see Table). Binding to S1P receptors elicits signal transduction through Gq-, Gi/o, G12-, G13-, and Rho-dependent pathways. Ligand-induced activation of $S1P_1$ and $S1P_3$ has been shown to promote angiogenesis, chemotaxis, and adherens junction assembly through Rac- and Rho-, *see* Lee, M.-J., S. Thangada, K.P. Claffey; N. Ancellin, C.H. Liu, M. Kluk, M. Volpi, R.I. Sha'afi, and T. Hla. 1999. *Cell.* 99:301-12, whereas agonism of $S1P_2$ promotes neurite retraction, *see* Van Brocklyn, J.R., Z. Tu, L.C. Edsall, R.R. Schmidt, and S. Spiegel. 1999. *J. Biol. Chem.* 274:4626-4632, and inhibits chemotaxis by blocking Rac activation, *see* Okamoto, H., N. Takuwa, T. Yokomizo, N. Sugimoto, S. Sakurada, H. Shigematsu, and Y. Takuwa. 2000. *Mol. Cell. Biol.* 20:9247-9261. $S1P_4$ is localized to hematopoietic cells and tissues, *see* Graeler, M.H., G. Bernhardt, and M. Lipp. 1999. *Curr. Top. Microbiol. Immunol.* 246:131-6, whereas $S1P_5$ is primarily a neuronal receptor with some expression in lymphoid tissue, *see* Im, D.S., C.E. Heise, N. Ancellin, B.F. O'Dowd, G.J. Shei, R.P. Heavens, M.R. Rigby, T. Hla, S. Mandala, G. McAllister, S.R. George, and K.R. Lynch. 2000. *J. Biol. Chem.* 275:14281-6. Administration of sphingosine 1-phosphate to animals induces systemic sequestration of peripheral blood lymphocytes into secondary lymphoid organs, stimulates FGF-mediated blood vessel growth and differentiation, *see* Lee, et al., supra, but also has cardiovascular effects that limit the utility of sphingosine 1-phosphate as a therapeutic agent, *see* Sugiyama, A., N.N. Aye, Y. Yatomi, Y. Ozaki, and K. Hashimoto. 2000. *Jpn. J. Pharmacol.* 82:338-342. The reduced heart rate and blood pressure measured with sphingosine 1-phosphate is associated with its non-selective, potent agonist activity on all S1P receptors.

The present invention encompasses compounds which are agonists of the $S1P_1$/Edg1 receptor having selectivity over the $S1P_3$/Edg3 receptor. An $S1P_1$/Edg1 receptor selective agonist has advantages over current therapies and extends the therapeutic window of lymphocytes sequestration agents, allowing better tolerability with higher dosing and thus improving efficacy as monotherapy.

While the main use for immunosuppressants is in treating bone marrow, organ and transplant rejection, other uses for such compounds include the treatment of arthritis, in particular, rheumatoid arthritis, insulin and non-insulin dependent diabetes, multiple sclerosis, psoriasis, inflammatory bowel disease, Crohn's disease, lupus erythematosis and the like.

Thus, the present invention is focused on providing immunosuppressant compounds that are safer and more effective than prior

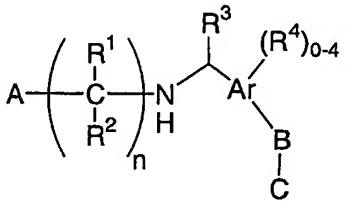
compounds. These and other objects will be apparent to those of ordinary skill in the art from the description contained herein.

Summary of S1P receptors

Name	Synonyms	Coupled G proteins	mRNA expression
$S1P_1$	Edg1, LP_{B1}	$G_{i/o}$	Widely distributed, endothelial cells
$S1P_2$	Edg5, LP_{B2}, AGR16, H218	$G_{i/o}$, G_q, $G_{12/13}$	Widely distributed, vascular smooth muscle cells
$S1P_3$	Edg3, LP_{B3}	$G_{i/o}$, G_q, $G_{12/13}$	Widely distributed, endothelial cells
$S1P_4$	Edg6, LP_{C1}	$G_{i/o}$	Lymphoid tissues, lymphocytic cell lines
$S1P_5$	Edg8, LP_{B4}, NRG1	$G_{i/o}$	Brain, spleen

SUMMARY OF THE INVENTION

The present invention encompasses compounds of Formula I:



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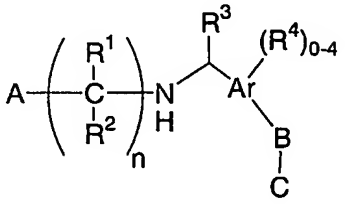
as well as the pharmaceutically acceptable salts and hydrates thereof. The compounds are useful for treating immune mediated diseases and conditions, such as bone marrow, organ and tissue transplant rejection. Pharmaceutical compositions and methods of use are included.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses a compound of Formula I



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or a pharmaceutically acceptable salt or hydrate thereof, wherein:

Ar is phenyl or naphthyl;

A is selected from: $-CO_2H$, 1*H*-tetrazol-5-yl, $-PO_3H_2$, $-PO_2H_2$, $-SO_3H$, and $-PO(R^5)OH$, wherein R^5 is selected from the group consisting of: C_{1-4}alkyl , hydroxyC_{1-4}alkyl, phenyl, $-C(O)-C_{1-3}$alkoxy and -CH(OH)-phenyl, said phenyl and phenyl portion of -CH(OH)-phenyl optionally substituted with 1-3 substituents independently selected from the group consisting of: hydroxy, halo, $-CO_2H$, C_{1-4}alkyl, $-S(O)_kC_{1-3}$alkyl, wherein k is 0, 1 or 2, C_{1-3}alkoxy, C_{3-6} cycloalkoxy, aryl and aralkoxy, the alkyl portions of said C_{1-4}alkyl, $-S(O)_kC_{1-3}$alkyl, C_{1-3}alkoxy and C_{3-6} cycloalkoxy optionally substituted with 1-3 halo groups;

n is 2, 3 or 4;

each R^1 and R^2 is each independently selected from the group consisting of: hydrogen, halo, hydroxy, $-CO_2H$, C_{1-6}alkyl and phenyl, said C_{1-6}alkyl and phenyl optionally substituted with 1-3 halo groups;

R^3 is selected from the group consisting of: hydrogen and C_{1-4}alkyl, optionally substituted with 1-3 hydroxy or halo groups;

each R^4 is independently selected from the group consisting of: hydroxy, halo,

$-CO_2H$, C_{1-4}alkyl, $-S(O)_kC_{1-3}$alkyl, wherein k is 0, 1 or 2, C_{1-3}alkoxy, C_{3-6} cycloalkoxy, aryl and aralkoxy, the alkyl portions of said C_{1-4}alkyl, $-S(O)_kC_{1-3}$alkyl, C_{1-3}alkoxy and C_{3-6} cycloalkoxy optionally substituted with 1-3 halo groups;

C is selected from the group consisting of:

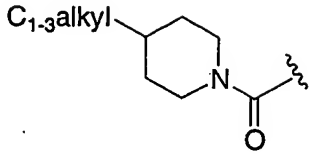
(1) C_{1-8}alkyl, C_{1-8}alkoxy, $-(C=O)-C_{1-6}$alkyl or $-CHOH-C_{1-6}$alkyl, said C_{1-8}alkyl, C_{1-8}alkoxy, $-(C=O)-C_{1-6}$alkyl and $-CHOH-C_{1-6}$alkyl optionally substituted with phenyl, and

(2) phenyl or HET, each optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, phenyl, C_{1-4}alkyl and C_{1-4}alkoxy, said C_{1-4}alkyl and C_{1-4}alkoxy groups optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from halo and hydroxy, and said phenyl optionally substituted with 1 to 5 groups independently selected from the group consisting of : halo and C_{1-4}alkyl, optionally substituted with 1-3 halo groups,

or **C** is not present;

when **C** is not present then **B** is selected from the group consisting of: phenyl, C_{5-16}alkyl, C_{5-16}alkenyl, C_{5-16}alkynyl, $-CHOH-C_{4-15}$alkyl, $-CHOH-C_{4-15}$alkenyl, $-CHOH-C_{4-15}$alkynyl, C_{4-15}alkoxy, $-O-C_{4-15}$alkenyl, $-O-C_{4-15}$alkynyl, C_{4-15}alkylthio, $-S-C_{4-15}$alkenyl, $-S-C_{4-15}$alkynyl, $-CH_2-C_{3-14}$alkoxy, $-CH_2-O-C_{3-14}$alkenyl, $-CH_2-O-C_{3-14}$alkynyl, $-(C=O)-C_{4-15}$alkyl, $-(C=O)-C_{4-15}$alkenyl, $-(C=O)-C_{4-15}$alkynyl, $-(C=O)-O-C_{3-14}$alkyl, $-(C=O)-O-C_{3-14}$alkenyl, $-(C=O)-O-C_{3-14}$alkynyl, $-(C=O)-N(R^6)(R^7)-C_{3-14}$alkyl, $-(C=O)-N(R^6)(R^7)-C_{3-14}$alkenyl, $-(C=O)-N(R^6)(R^7)-C_{3-14}$alkynyl, $-N(R^6)(R^7)-(C=O)-C_{3-14}$alkyl, $-N(R^6)(R^7)-(C=O)-C_{3-14}$alkenyl and $-N(R^6)(R^7)-(C=O)-C_{3-14}$alkynyl,

when **C** is phenyl or HET then **B** is selected from the group consisting of: C_{1-6}alkyl, C_{1-5}alkoxy, $-(C=O)-C_{1-5}$alkyl, $-(C=O)-O-C_{1-4}$alkyl, $-(C=O)-N(R^6)(R^7)-C_{1-4}$alkyl,



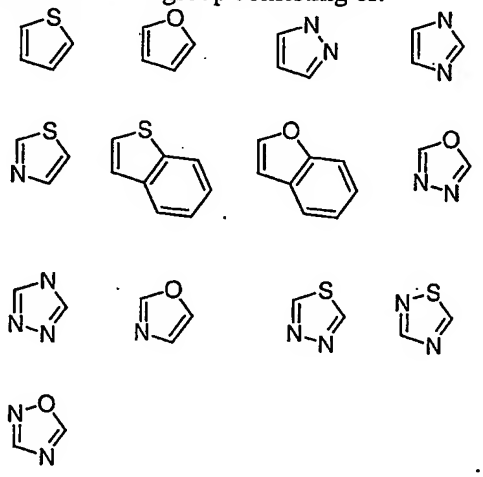
, phenyl and HET, and

when **C** is C_{1-8}alkyl, C_{1-8}alkoxy, -(C=O)-C_{1-6}alkyl or –CHOH-C_{1-6}alkyl then **B** is phenyl; and

R^6 and R^7 are independently selected from the group consisting of: hydrogen, C_{1-9}alkyl and -$(CH_2)_p$-phenyl, wherein p is 1 to 5 and phenyl is optionally substituted with 1-3 substituents independently selected from the group consisting of: C_{1-3}alkyl and C_{1-3}alkoxy, each optionally substituted with 1-3 halo groups.

For purposes of this specification, **C** may be substituted at any substitutable position on **B**. For example, when **B** is methoxy and **C** is thiophene, thiophene replaces a hydrogen on the methoxy group. Further variations are illustrated in the examples that follow. Also, the point of any attachments shown for **B** is to the Ar group. For example, when **B** is -(C=O)-C_{6-11}alkynyl this means **B** is attached to Ar as follows: Ar-(C=O)-C_{6-11}alkynyl. **C** may then be substituted at any substituable position on **B**.

An embodiment of the invention encompasses a compound of Formula I wherein HET is selected from the group consisting of:



For purposes of this specification HET can be attached at any point of attachment and substituents can be substituted at any substituable position. Such points of attachments and substituable positions are ascertainable to one having ordinary skill in the art.

An embodiment of the invention encompasses a compound of Formula I wherein n is 2.

An embodiment of the invention encompasses a compound of Formula I wherein n is 3.

An embodiment of the invention encompasses a compound of Formula I wherein each R^1 and R^2 is independently selected from the group consisting of: hydrogen, $-CO_2H$, hydroxy, halo, C_{1-3}alkyl and phenyl.

An embodiment of the invention encompasses a compound of Formula I wherein **A** is PO_3H_2.

An embodiment of the invention encompasses a compound of Formula I wherein **A** is $-CO_2H$.

An embodiment of the invention encompasses a compound of Formula I wherein **A** is $PO(R^5)OH$, wherein R^5 is selected from the group consisting of: C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C(O)-C_{1-2}alkoxy and benzyl, wherein both the methyl and phenyl portions of said benzyl are optionally substituted with 1-3 halo or hydroxy groups.

An embodiment of the invention encompasses a compound of Formula I wherein **A** is PO_2H_2.

An embodiment of the invention encompasses a compound of Formula I wherein **A** is 1*H*-tetrazol-5-yl.

An embodiment of the invention encompasses a compound of Formula I wherein R^3 is hydrogen or methyl.

An embodiment of the invention encompasses a compound of Formula I wherein each R^4 is independently selected from the group consisting of: halo, hydroxy, C1-3alkyl, C1-3alkoxy, C1-3alkylthio, phenyl, benzyloxy and cyclopropyloxy.

An embodiment of the invention encompasses a compound of Formula I wherein **B** is C_{8-10}alkyl and **C** is not present.

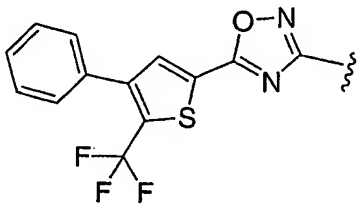
An embodiment of the invention encompasses a compound of Formula I wherein **B** is C_{4-11}alkoxy and **C** is not present.

An embodiment of the invention encompasses a compound of Formula I wherein **B** is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, C_{1-4}alkyl and C_{1-4}alkoxy, and **C** is selected from the group consisting of: hydrogen, phenyl, C_{1-8}alkyl, C_{1-8}alkoxy, -(C=O)-C_{1-6}alkyl and –CHOH-C_{1-6}alkyl, said C_{1-8}alkyl, C_{1-8}alkoxy, -(C=O)-C_{1-6}alkyl and –CHOH-C_{1-6}alkyl optionally substituted with phenyl.

An embodiment of the invention encompasses a compound of Formula I wherein **B** is selected from the group consisting of: -CHOH-C_{6-10}alkyl, C_{6-10}alkylthio, -CH_2-C_{5-9}alkoxy, -(C=O)-C_{6-10}alkyl, -(C=O)-O-C_{5-9}alkyl, -(C=O)-N(R^6)(R^7)-C_{5-9}alkyl, -N(R^6)(R^7)-(C=O)-C_{5-9}alkyl, and **C** is not present.

An embodiment of the invention encompasses a compound of Formula I wherein **B** is C_{1-6}alkyl or C_{1-5}alkoxy and **C** is phenyl.

An embodiment of the invention encompasses a compound of Formula I wherein **B-C** is



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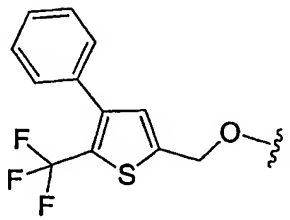
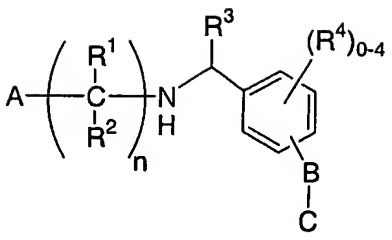


An embodiment of the invention encompasses a compound of Formula I wherein Ar is phenyl and the group –**B-C** is attached to the phenyl ring at the 3- or 4-position.

An embodiment of the invention encompasses a compound of Formula II



II

or a pharmaceutically acceptable salt or hydrate thereof, wherein

the group **–B-C** is attached to the phenyl ring at the 3- or 4-position;

n is 2, 3 or 4;

each R^1 and R^2 is independently selected from the group consisting of: hydrogen, -CO_2H, hydroxy, halo, C_{1-3}alkyl and phenyl, said C1-3alkyl and phenyl optionally substituted with 1-3 halo group;

A is selected from the group consisting of: 1*H*-tetrazol-5-yl, PO_2H_2, PO_3H_2, $-CO_2H$ and $PO(R^5)OH$, wherein R^5 is selected from the group consisting of: C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C(O)-C_{1-2}alkoxy and benzyl, wherein both the methyl and phenyl portions of said benzyl are optionally substituted with 1-3 halo or hydroxy groups;

R^3 is hydrogen or methyl;

each R^4 is independently selected from the group consisting of: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, phenyl, benzyloxy and cyclopropyloxy; and

B-C is selected from the group consisting of:

(1) **B** is C_{8-10}alkyl and **C** is not present.

(2) **B** is C_{4-11}alkoxy and **C** is not present.

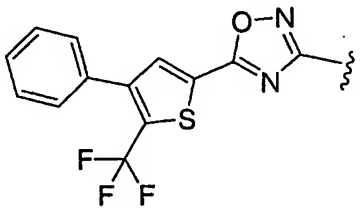
(3) **B** is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, C_{1-4}alkyl and C_{1-4}alkoxy, and **C** is selected from the group consisting of: hydrogen, phenyl, C_{1-8}alkyl, C_{1-}

8alkoxy, -(C=O)-C_{1-6}alkyl and –CHOH-C_{1-6}alkyl, said C_{1-8}alkyl, C_{1-8}alkoxy, -(C=O)-C_{1-6}alkyl and –CHOH-C_{1-6}alkyl optionally substituted with phenyl;

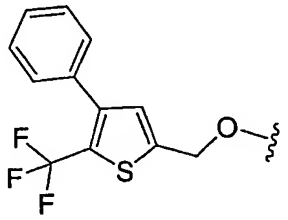
(4) **B** is -CHOH-C_{6-10}alkyl, C_{6-10}alkylthio, -CH_2-C_{5-9}alkoxy, -(C=O)-C_{6-10}alkyl, -(C=O)-O-C_{5-9}alkyl, -(C=O)-N(R^6)(R^7)-C_{5-9}alkyl or -N(R^6)(R^7)-(C=O)-C_{5-9}alkyl, and **C** is not present.

(5) **B** is C_{1-6}alkyl or C_{1-5}alkoxy and **C** is phenyl.

(6) **B-C** is



or



The invention also encompasses a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound of Formula I in an amount that is effective for treating said immunoregulatory abnormality.

Within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is an autoimmune or chronic inflammatory disease selected from the group consisting of: systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy and asthma.

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is bone marrow or organ transplant rejection or graft-versus-host disease.

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is selected from the group consisting of: transplantation of organs or tissue, graft-versus-host diseases brought about by transplantation, autoimmune syndromes including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne, alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma, Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium,

alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, and chronic bacterial infection

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is multiple sclerosis

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is rheumatoid arthritis

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is systemic lupus erythematosus

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is psoriasis

Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is rejection of transplanted organ or tissue

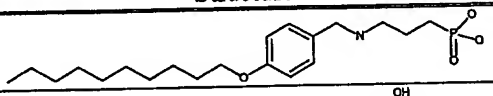
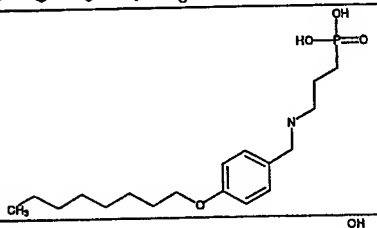
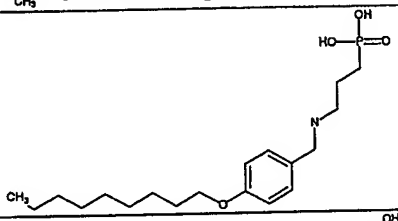
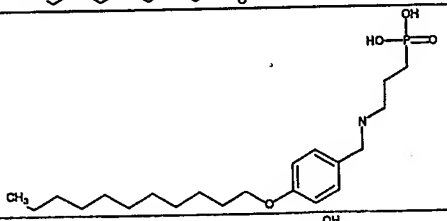
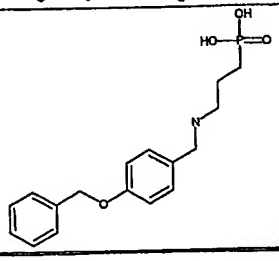
Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is inflammatory bowel disease.

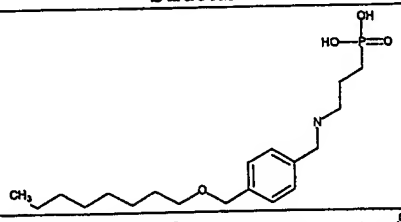
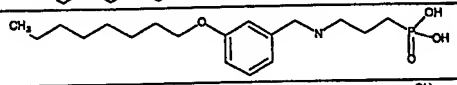
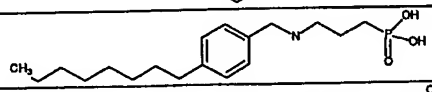
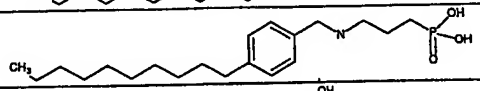
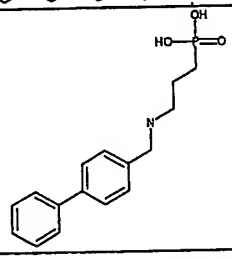
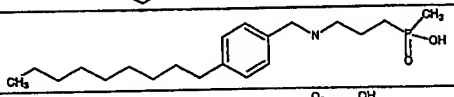
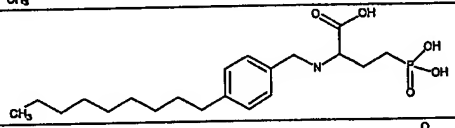
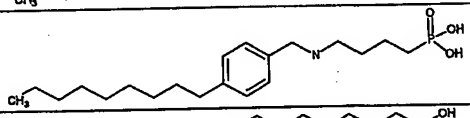
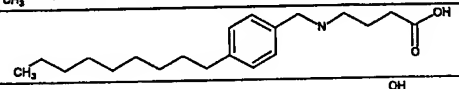
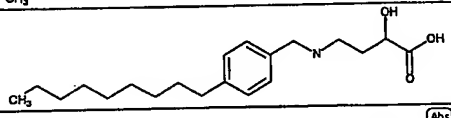
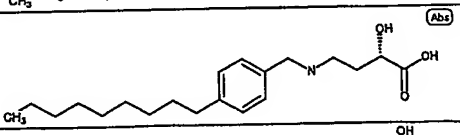
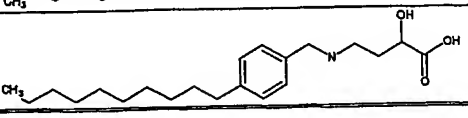
Also within this embodiment is encompassed the above method wherein the immunoregulatory abnormality is a malignancy of lymphoid origin including acute and chronic lymphocytic leukemias and lymphomas.

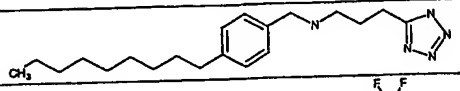
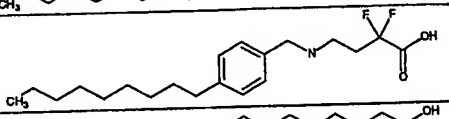
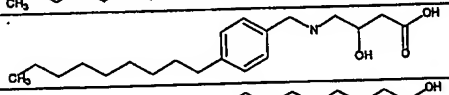
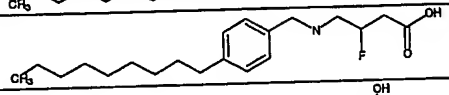
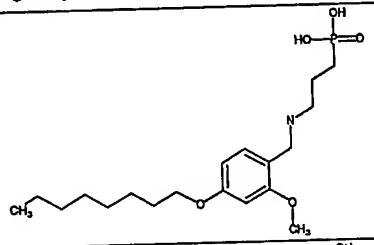
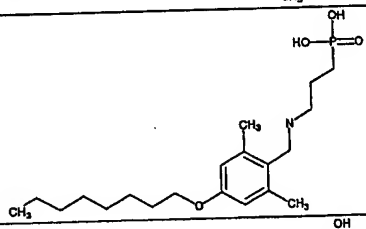
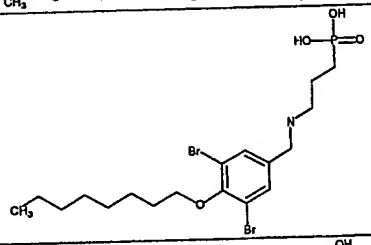
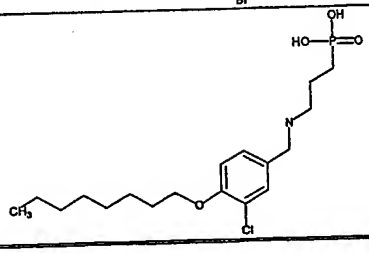
The invention also encompasses a method of suppressing the immune system in a mammalian patient in need of immunosuppression comprising administering to said patient an immunosuppressing effective amount of a compound of Formula I.

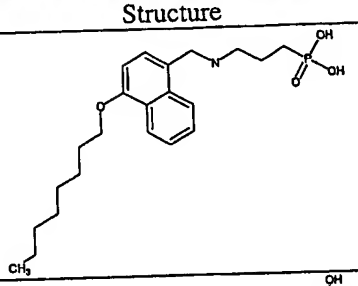
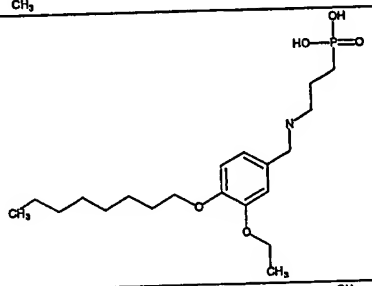
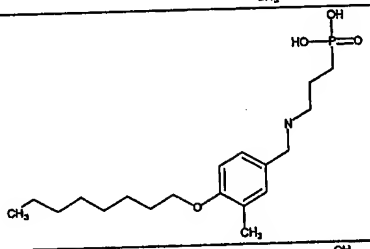
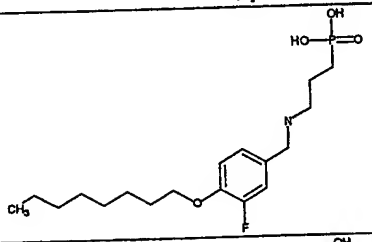
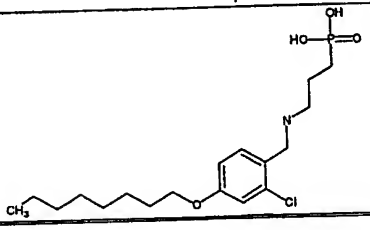
The invention also encompasses a pharmaceutical composition comprised of a compound of Formula I in combination with a pharmaceutically acceptable carrier.

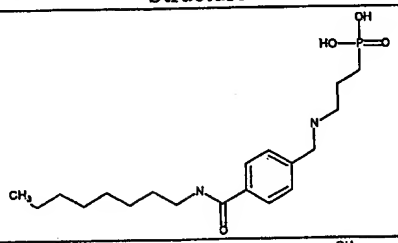
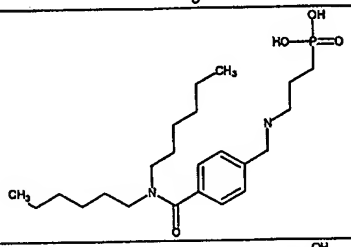
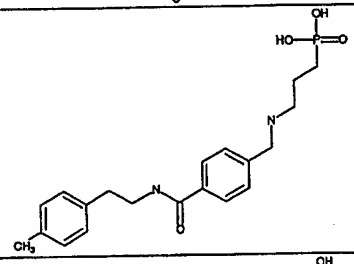
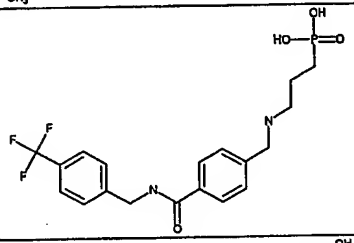
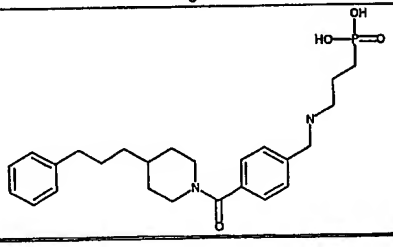
Exemplifying the invention are the following compounds:

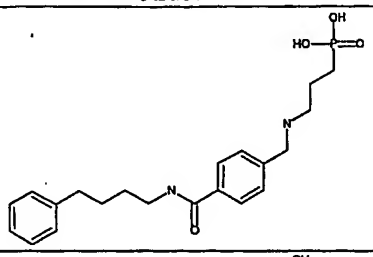
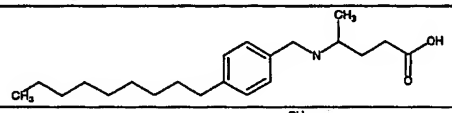
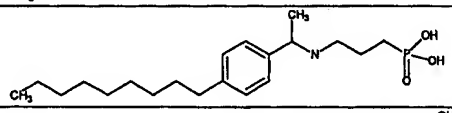
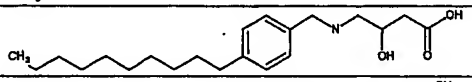
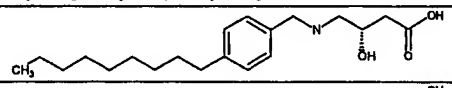
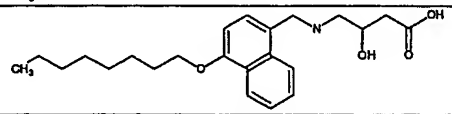
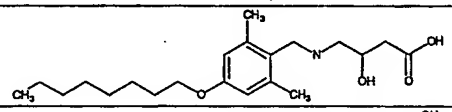
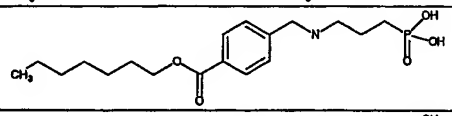
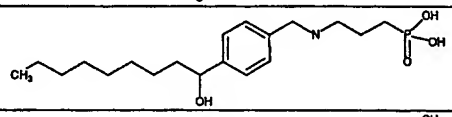
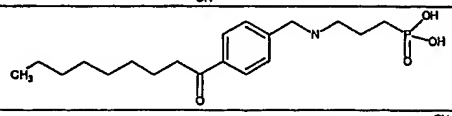
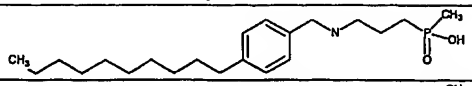
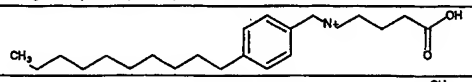
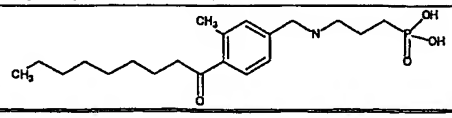
Example Number	Structure
1	
2	
3	
4	
5	

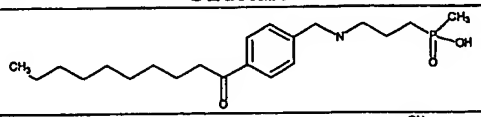
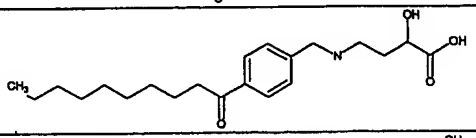
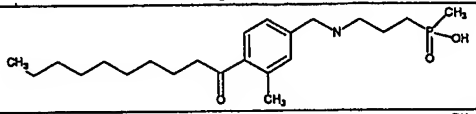
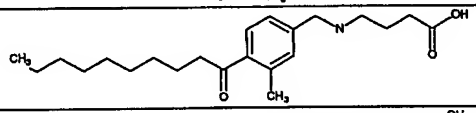
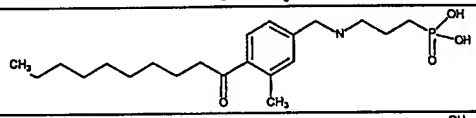
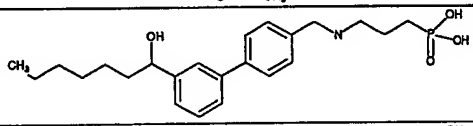
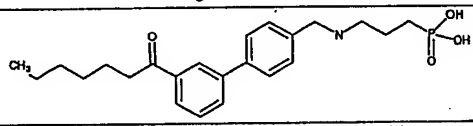
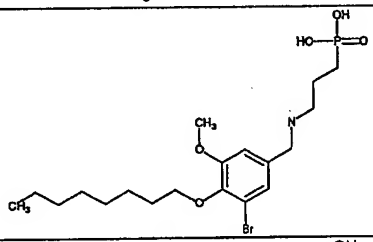
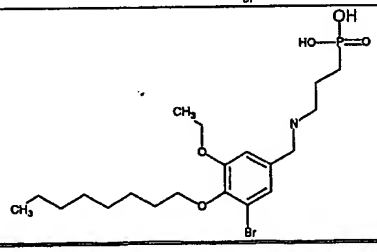
Example Number	Structure
6	
7	
8	
9	
11	
12	
13	
14	
15	
16	
17	
18	

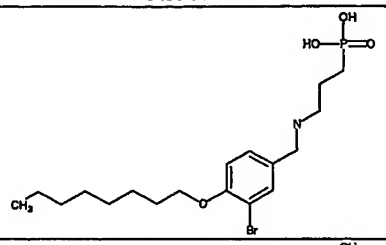
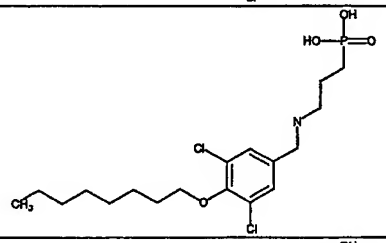
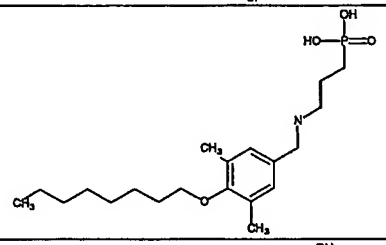
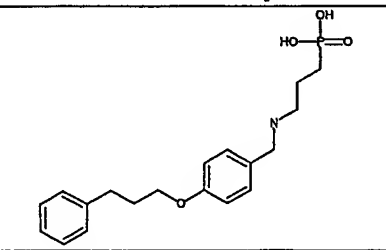
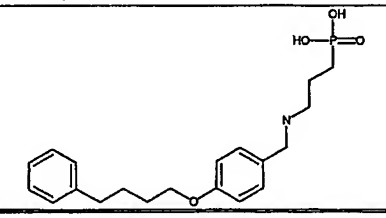
Example Number	Structure
19	
20	
21	
22	
23	
24	
25	
26	

Example Number	Structure
27	
28	
29	
30	
31	

Example Number	Structure
32	
33	
34	
35	
36	

Example Number	Structure
37	
38	
39	
40	
41	
43	
44	
45	
46	
47	
48	
49	
50	

Example Number	Structure
51	
52	
53	
54	
55	
56	
57	
58	
59	

Example Number	Structure
60	
61	
62	
63	
64	

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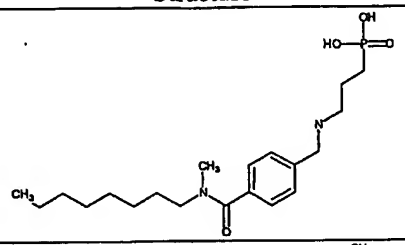
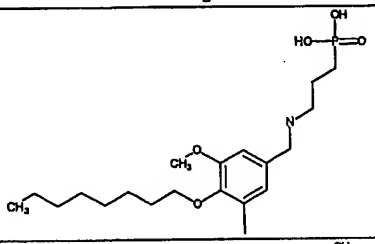
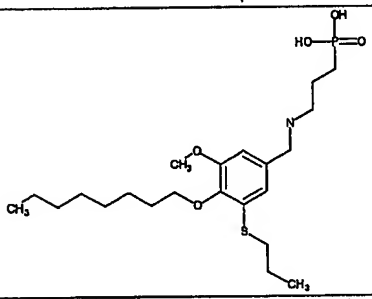
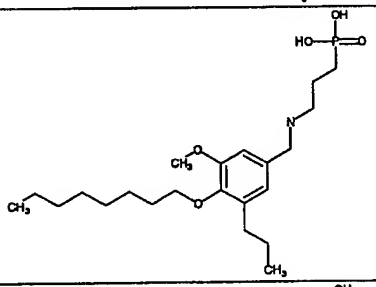
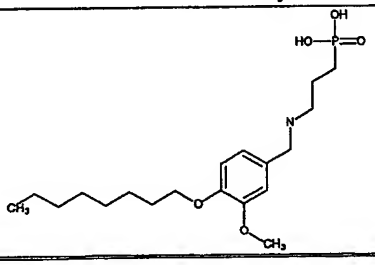
65	
66	
67	
68	
69	

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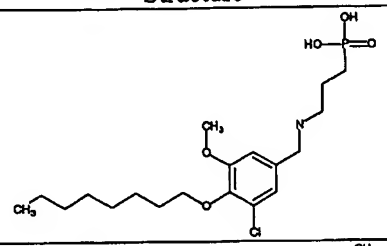
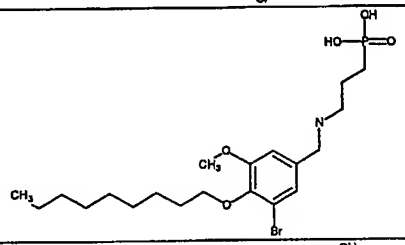
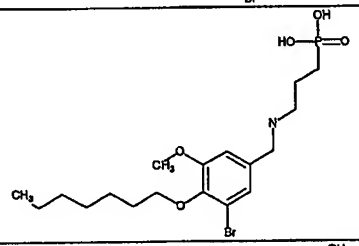
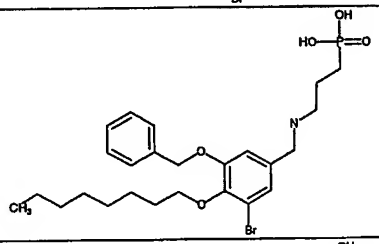
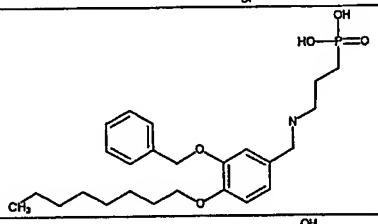
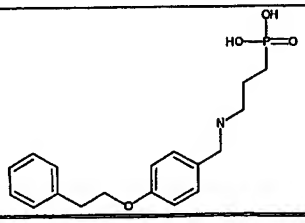
70	
71	
72	
73	
74	
75	

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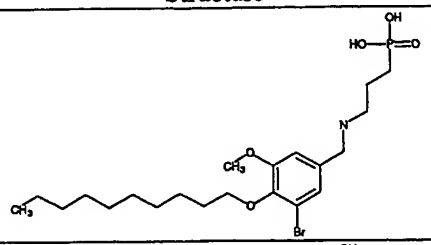
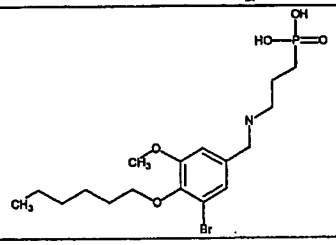
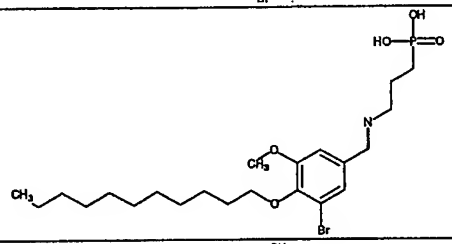
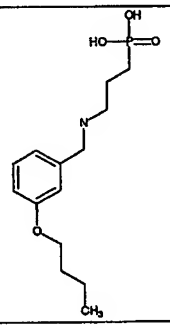
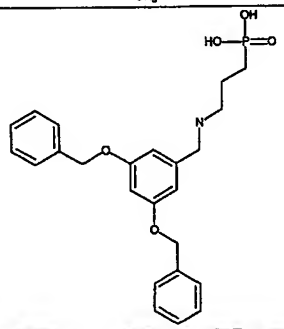
76	
77	
78	
79	
80	

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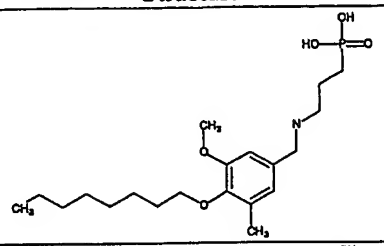
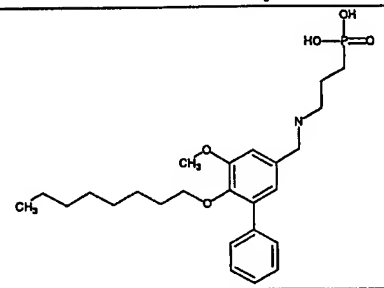
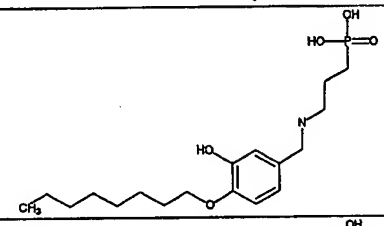
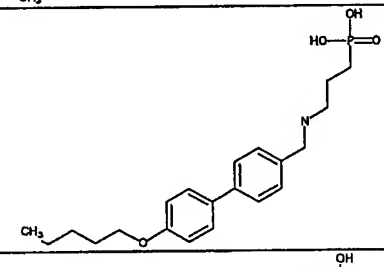
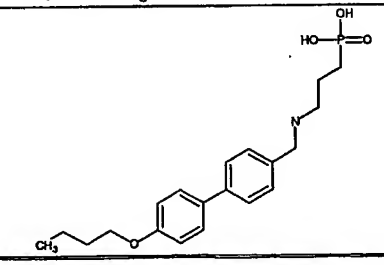
81	
82	
83	
84	
85	

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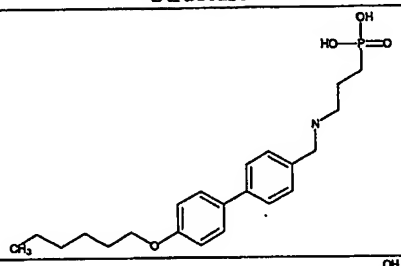
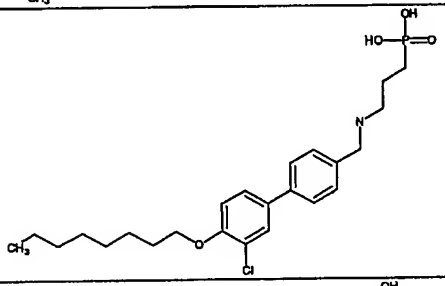
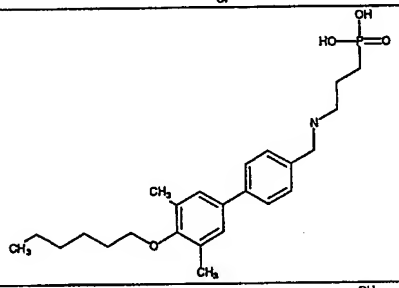
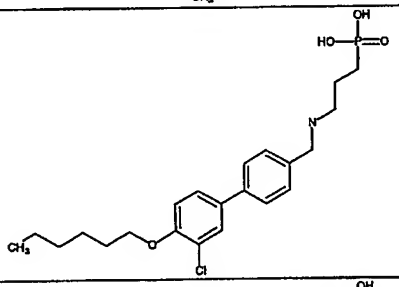
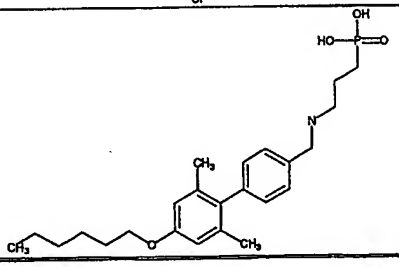
86	
87	
88	
89	
90	

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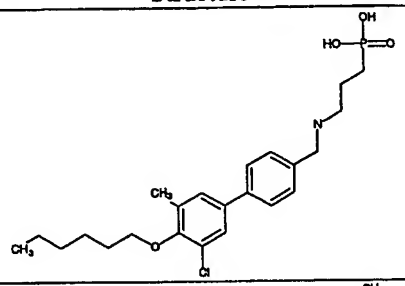
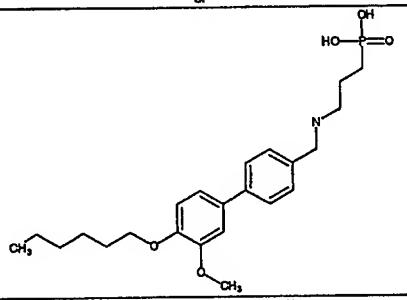
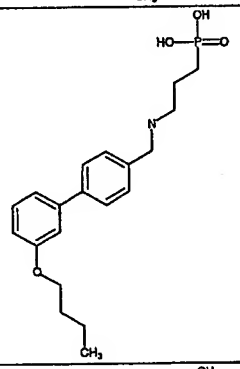
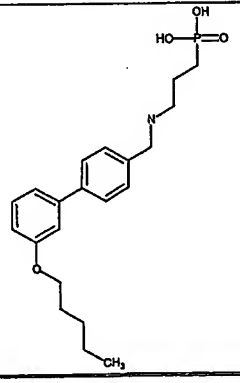
91	
92	
93	
94	

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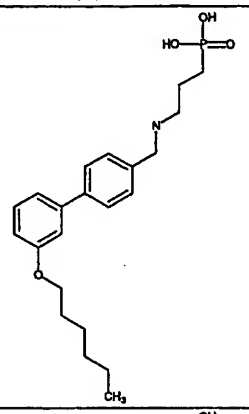
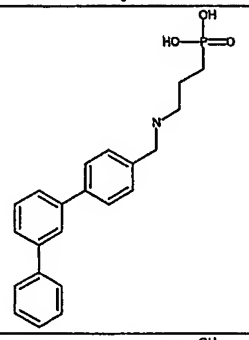
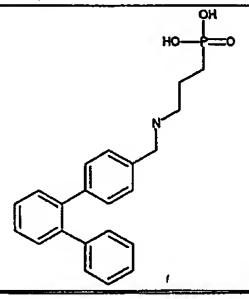
95	
96	
97	

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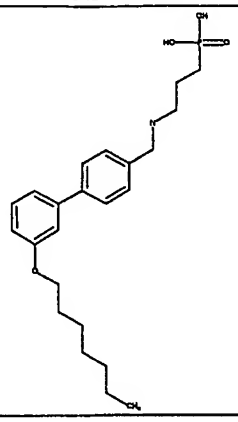
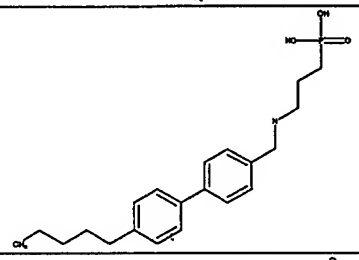
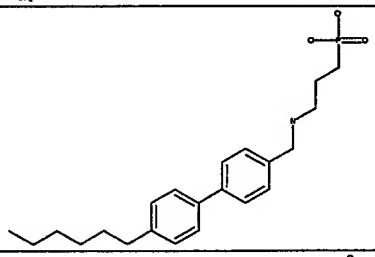
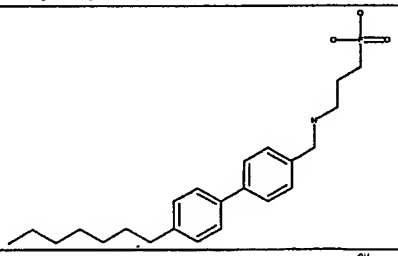
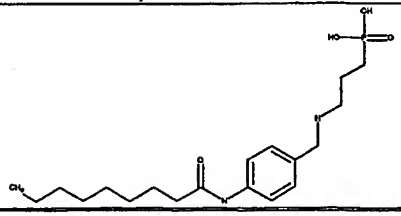
98	
99	
100	
101	
102	

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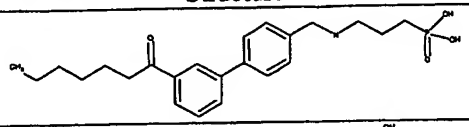
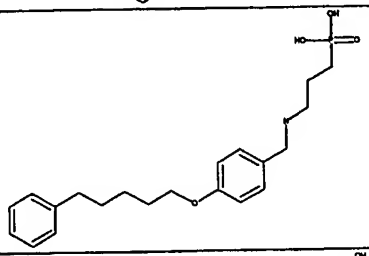
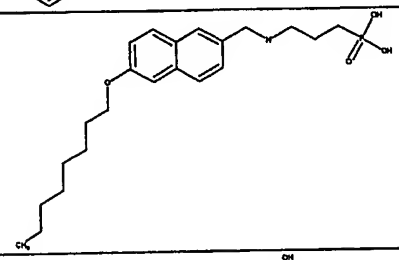
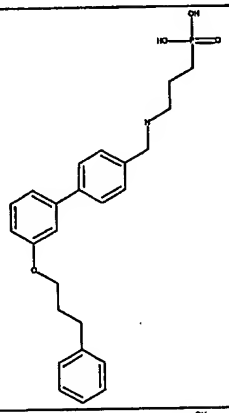
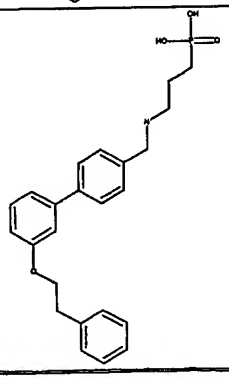
103	
104	
105	
106	
107	

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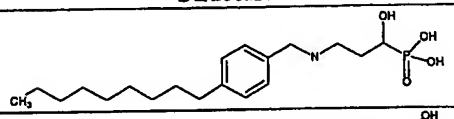
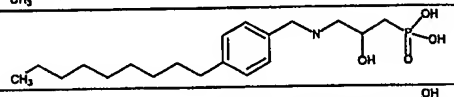
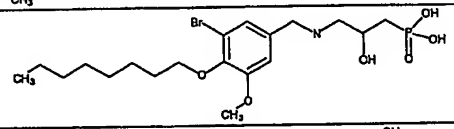
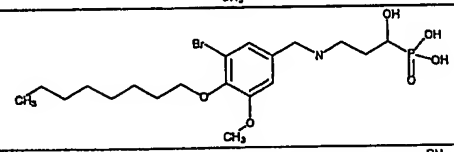
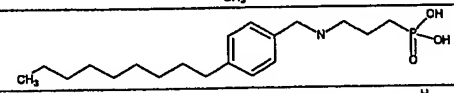
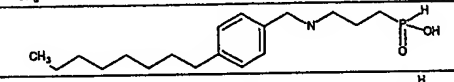
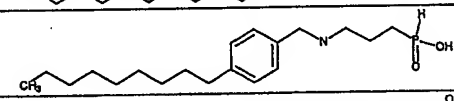
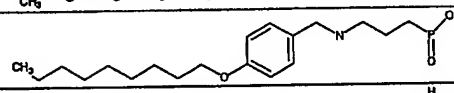
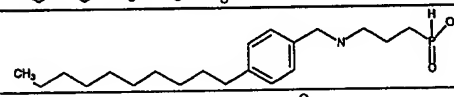
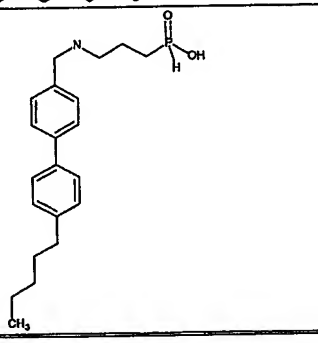
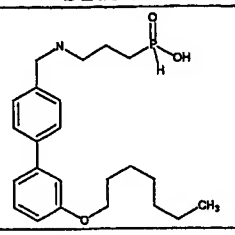
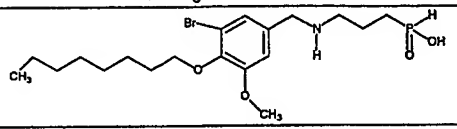
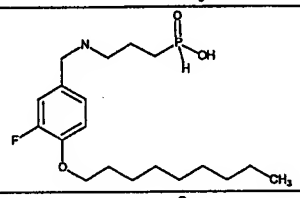
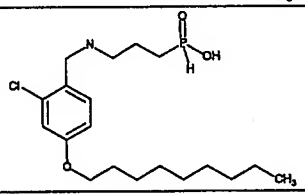
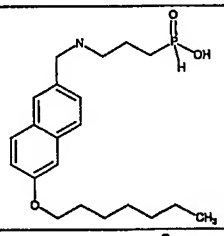
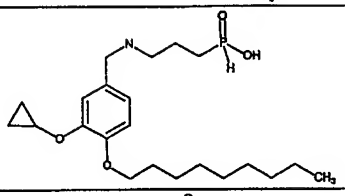
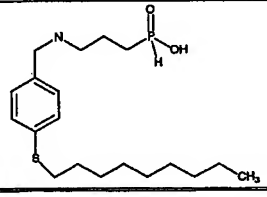
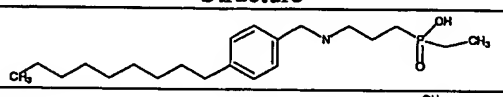
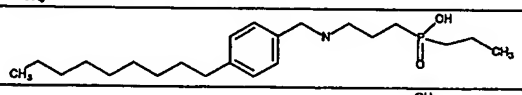
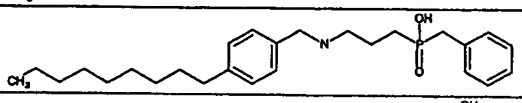
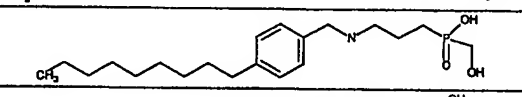
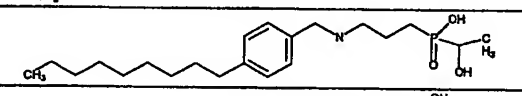
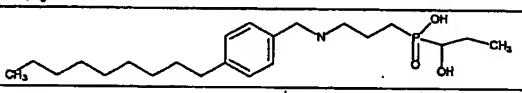
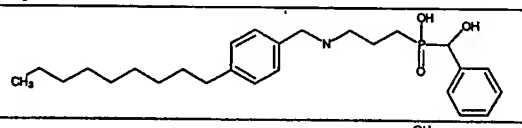
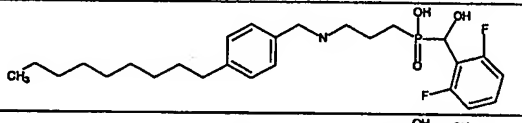
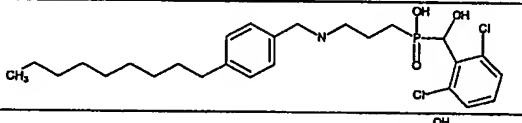
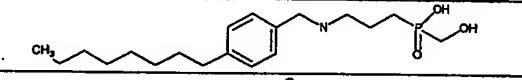
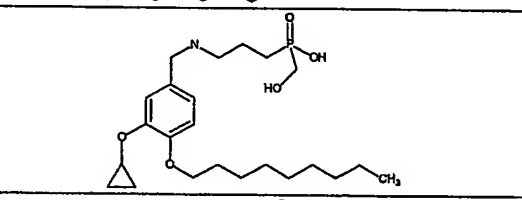
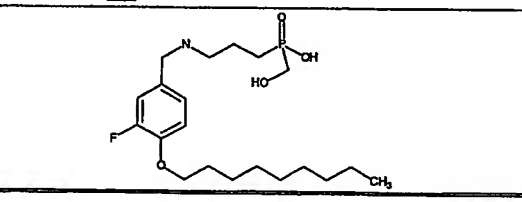
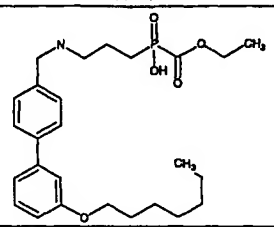
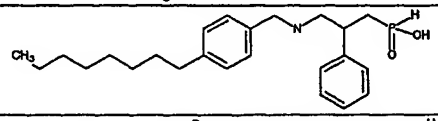
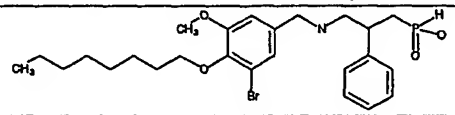
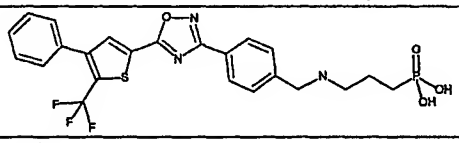
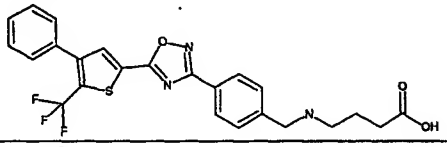
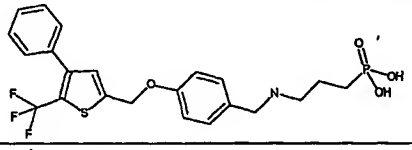
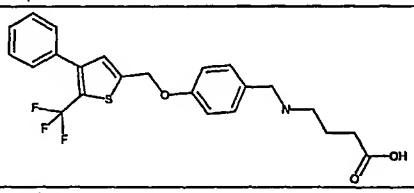
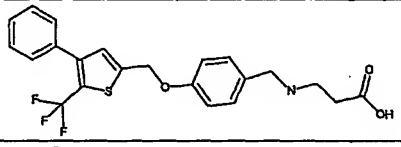
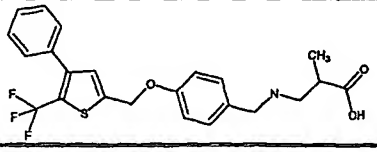
108	
109	
110	
111	
112	
113	
114	
115	
116	
117	

Example Number	Structure
118	
119	
120	
121	
122	
123	
124	

Example Number	Structure
125	
126	
127	
128	
129	
130	
131	
132	
133	
134	
135	
136	

Example Number	Structure
137	
138	
139	
140	
141	
142	
143	
144	
145	

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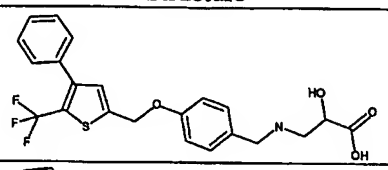
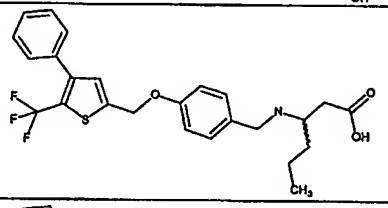
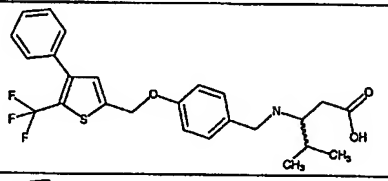
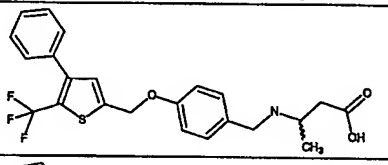
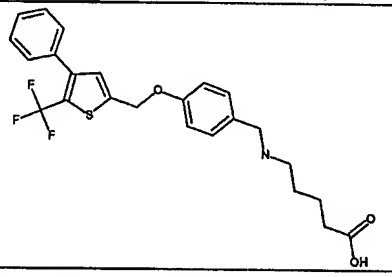
146	
147	
148	
149	
150	

The invention is described using the following definitions unless otherwise indicated.

The term "halogen" or "halo" includes F, Cl, Br, and I.

The term "alkyl" means linear or branched structures and combinations thereof, having the indicated number of carbon atoms. Thus, for example, C_{1-6}alkyl includes methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "alkoxy" means alkoxy groups of a straight, branched or cyclic configuration having the indicated number of carbon atoms. C_{1-6}alkoxy, for example, includes methoxy, ethoxy, propoxy, isopropoxy, and the like.

The term "alkylthio" means alkylthio groups having the indicated number of carbon atoms of a straight, branched or cyclic configuration. C_{1-6}alkylthio, for example, includes methylthio, propylthio, isopropylthio, and the like.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon-to-carbon double bond. C_{2-6}alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

The term "alkynyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon triple bond. C_{3-6}alkynyl, for example, includes , propenyl, 1-methylethenyl, butenyl and the like.

The term "cycloalkyl" means mono-, bi- or tri-cyclic structures, optionally combined with linear or branched structures, the indicated number of carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclopentyl, cycloheptyl, adamantyl, cyclododecylmethyl, 2-ethyl-1- bicyclo[4.4.0]decyl, and the like.

The term "aryl" is defined as a mono- or bi-cyclic aromatic ring system and includes, for example, phenyl, naphthyl, and the like.

The term "aralkyl" means an alkyl group as defined above of 1 to 6 carbon atoms with an aryl group as defined above substituted for one of the alkyl hydrogen atoms, for example, benzyl and the like.

The term "aryloxy" means an aryl group as defined above attached to a molecule by an oxygen atom (aryl-O) and includes, for example, phenoxy, naphthoxy and the like.

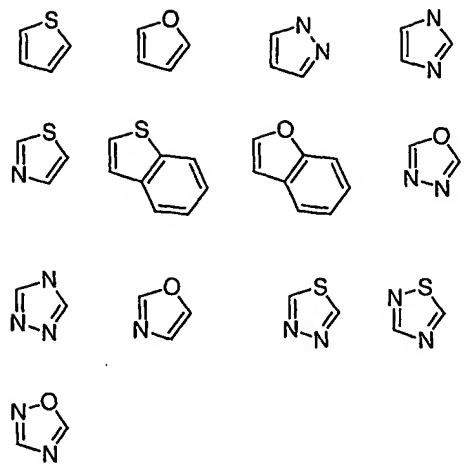
The term "aralkoxy" means an aralkyl group as defined above attached to a molecule by an oxygen atom (aralkyl-O) and includes, for example, benzyloxy, and the like.

The term "arylthio" is defined as an aryl group as defined above attached to a molecule by an sulfur atom (aryl-S) and includes, for example, thiophenyoxy, thionaphthoxy and the like.

The term "aroyl" means an aryl group as defined above attached to a molecule by an carbonyl group (aryl-C(O)-) and includes, for example, benzoyl, naphthoyl and the like.

The term "aroyloxy" means an aroyl group as defined above attached to a molecule by an oxygen atom (aroyl-O) and includes, for example, benzoyloxy or benzoxy, naphthoyloxy and the like.

The term "HET" is defined as a 5- to 10-membered aromatic, partially aromatic or non-aromatic mono- or bicyclic ring, containing 1-5 heteroatoms selected from O, S and N, and optionally substituted with 1-2 oxo groups. Preferably, "HET" is a 5- or 6-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N, for example, pyridine, pyrimidine, pyridazine, furan, thiophene, thiazole, oxazole, isooxazole and the like, or heterocycle is a 9- or 10-membered aromatic or partially aromatic bicyclic ring containing 1-3 heteroatoms selected from O, S, and N, for example, benzofuran, benzothiophene, indole, pyranopyrrole, benzopyran, quionoline, benzocyclohexyl, naphtyridine and the like. "HET" also includes the following: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl. A preferred group of HET is as follows:



The term "treating" encompasses not only treating a patient to relieve the patient of the signs and symptoms of the disease or condition but also prophylactically treating an asymptomatic patient to prevent the onset or progression of the disease or condition. The term "amount effective for treating" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term also encompasses the amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician.

The invention described herein includes pharmaceutically acceptable salts and hydrates. Pharmaceutically acceptable salts include both the metallic (inorganic) salts and organic salts; a list of which is given in *Remington's Pharmaceutical Sciences*, 17th Edition, pg. 1418 (1985). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydroscopicity and solubility. As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not limited to salts of inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate or salts of an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate or pamoate, salicylate and stearate. Similarly pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium,

aluminum, lithium and ammonium (especially ammonium salts with secondary amines). Preferred salts of this invention for the reasons cited above include potassium, sodium, calcium and ammonium salts. Also included within the scope of this invention are crystal forms, hydrates and solvates of the compounds of Formula I.

For purposes of this Specification, "pharmaceutically acceptable hydrate" means the compounds of the instant invention crystallized with one or more molecules of water to form a hydrated form.

The invention also includes the compounds falling within formula I in the form of one or more stereoisomers, in substantially pure form or in the form of a mixture of stereoisomers. All such isomers are encompassed within the present invention.

By virtue of their $S1P_1$/Edg1 agonist activity, the compounds of the present invention are immunoregulatory agents useful for treating or preventing automimmune or chronic inflammatory diseases. The compounds of the present invention are useful to suppress the immune system in instances where immunosuppression is in order, such as in bone marrow, organ or transplant rejection, autoimmune and chronic inflammatory diseases, including systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy and asthma.

More particularly, the compounds of the present invention are useful to treat or prevent a disease or disorder selected from the group consisting of: transplantation of organs or tissue, graft-versus-host diseases brought about by transplantation, autoimmune syndromes including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne, alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves'

opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma, Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C_4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of

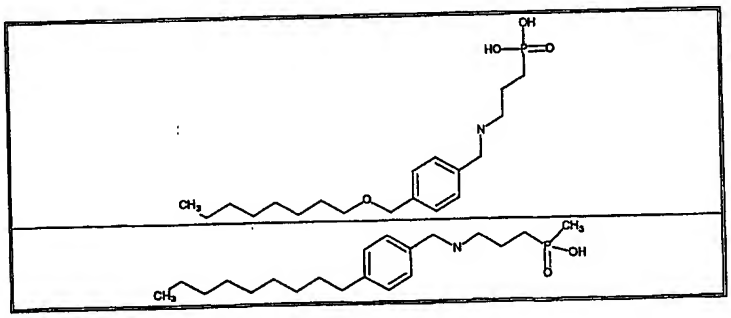
chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, and chronic bacterial infection.

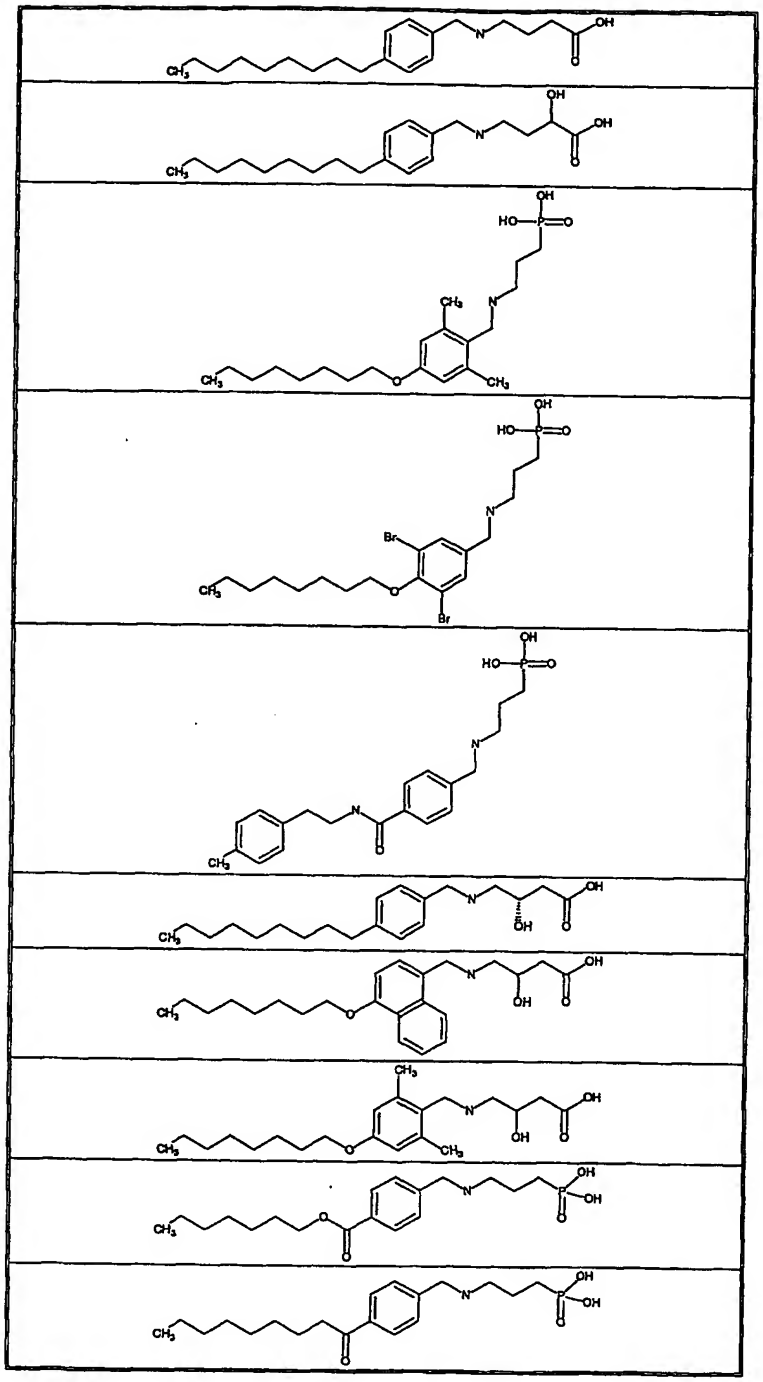
Also embodied within the present invention is a method of preventing or treating resistance to transplantation or transplantation rejection of organs or tissues in a mammalian patient in need thereof, which comprises administering a therapeutically effective amount of the compound of Formula I.

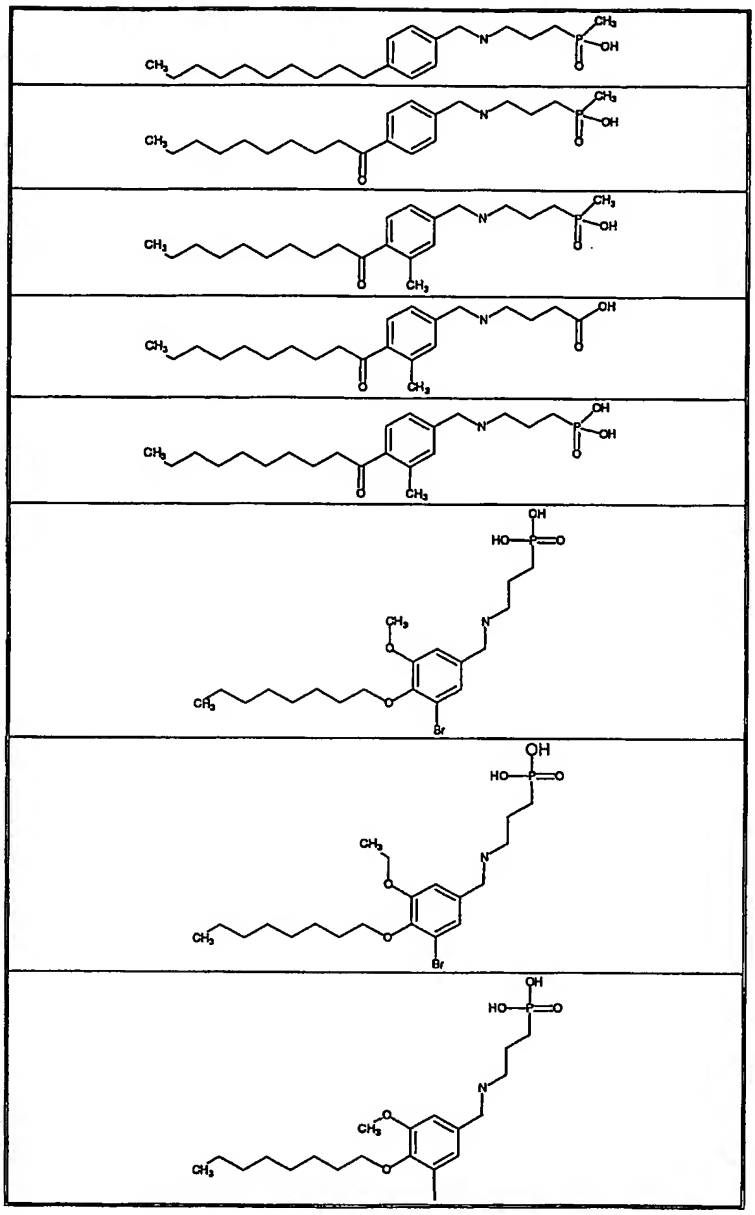
A method of suppressing the immune system in a mammalian patient in need thereof, which comprises administering to the patient an immune system suppressing amount of the compound of Formula I is yet another embodiment.

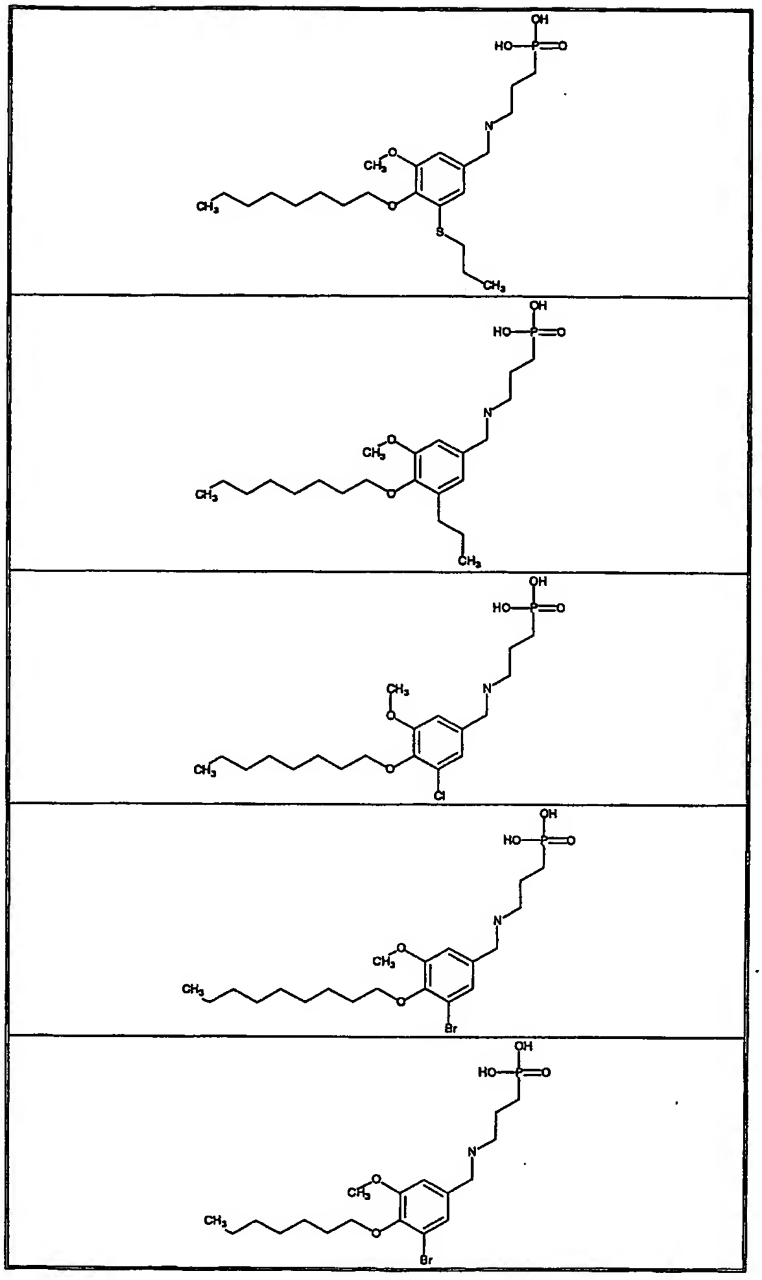
Most particularly, the method described herein encompasses a method of treating or preventing bone marrow or organ transplant rejection which is comprised of admininstering to a mammalian patient in need of such treatment or prevention a compound of formula I, or a pharmaceutically acceptable salt or hydrate thereof, in an amount that is effective for treating or preventing bone marrow or organ transplant rejection.

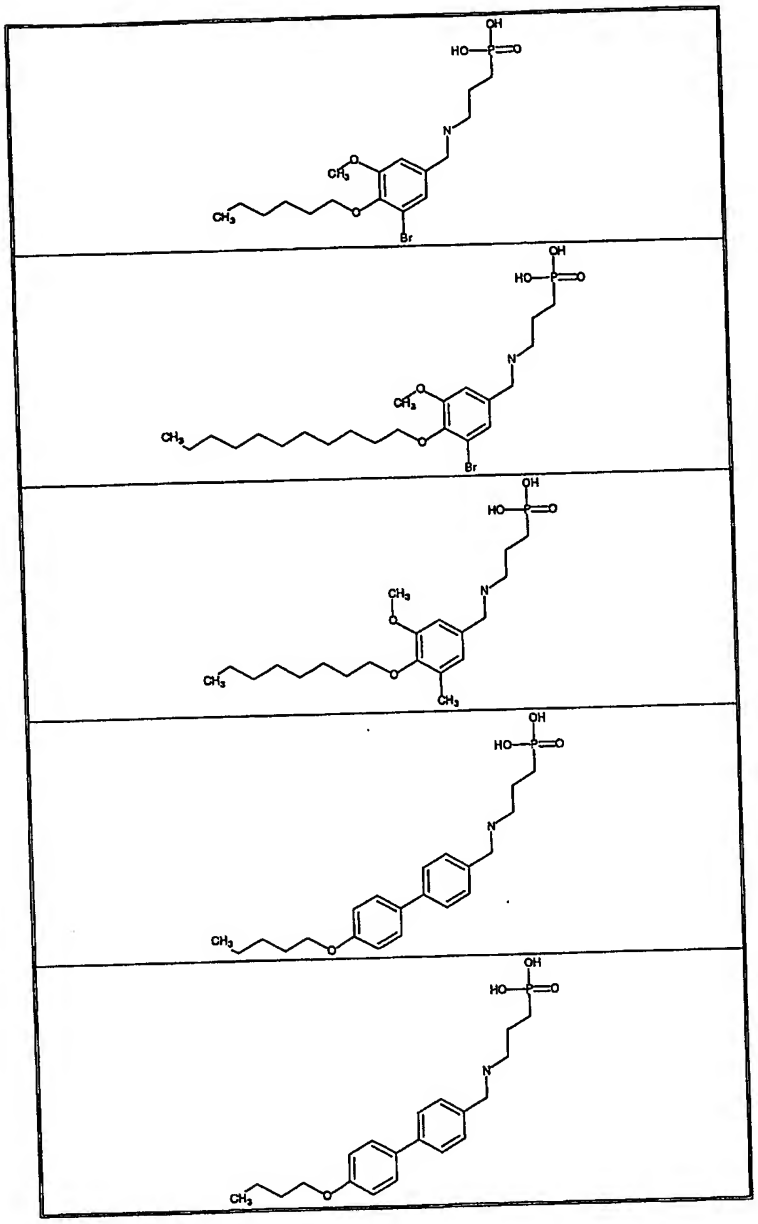
Furthermore, a preferred group of compounds of the present invention are agonists of the $S1P_1$/Edg1 receptor having selectivity over $S1P_3$/Edg3 receptor. An Edg1 selective agonist has advantages over current therapies and extends the therapeutic window of lymphocytes sequestration agents, allowing better tolerability with higher dosing and thus improving efficacy as monotherapy. The following compounds possesses a selectivity for the S1P1/Edg1 receptor over the $S1PR_3$/Edg3 receptor of at least 20 fold as measured by the ratio of EC_{50} for the $S1P_1$/Edg1 receptor to the EC_{50} for the $S1P_3$/Edg3 receptor as evaluated in the ^{35}S-GTPγS binding assay and possesses an EC_{50} for binding to the $S1P_1$/Edg1 receptor of 100 nM or less as evaluated by the ^{35}S-GTPγS binding assay:

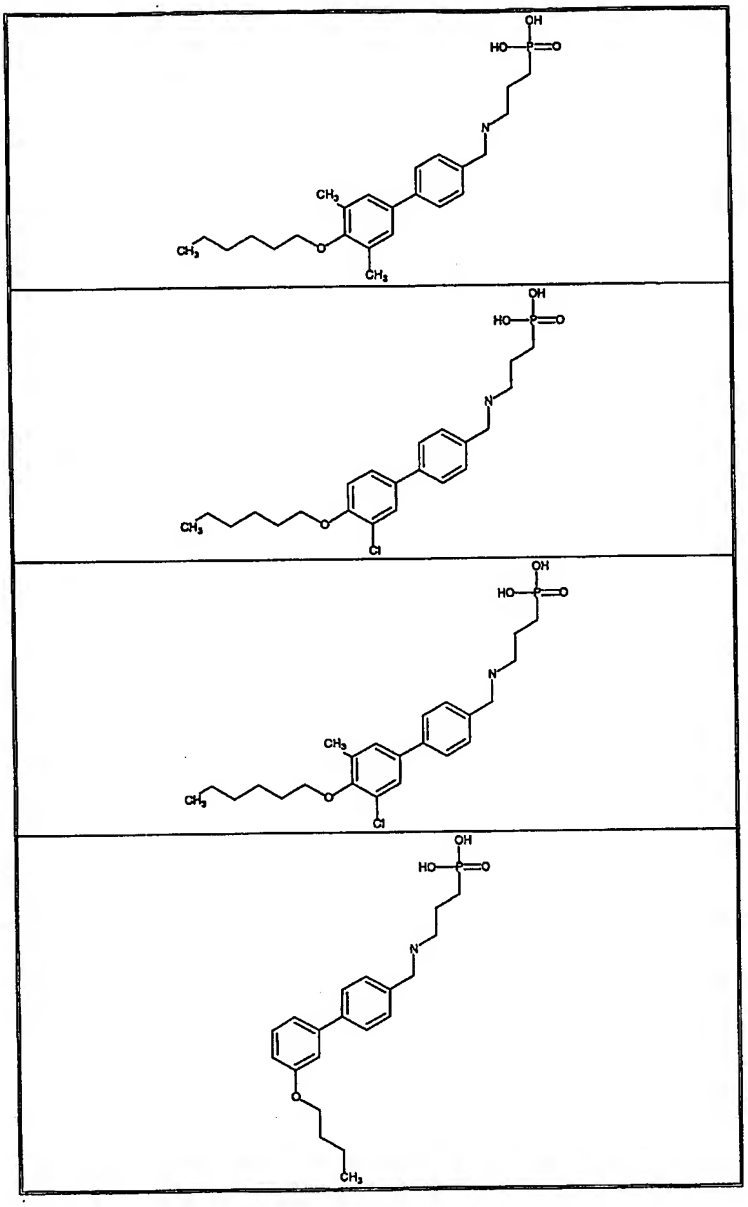


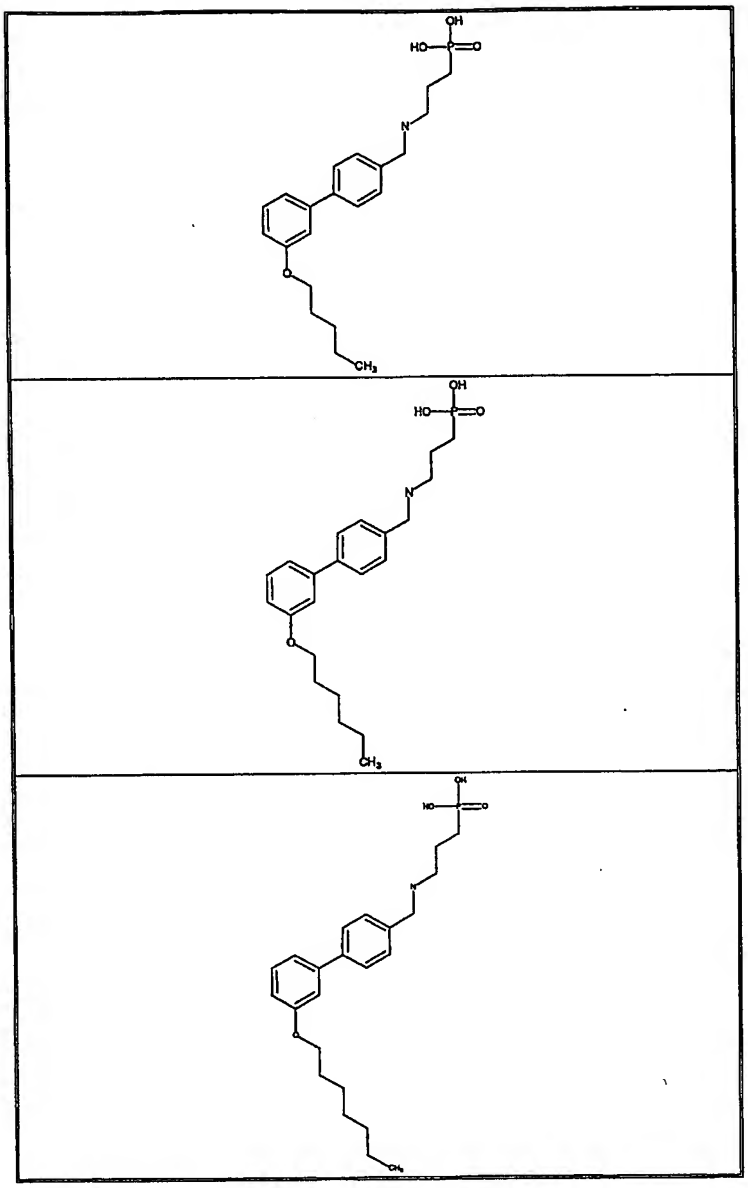


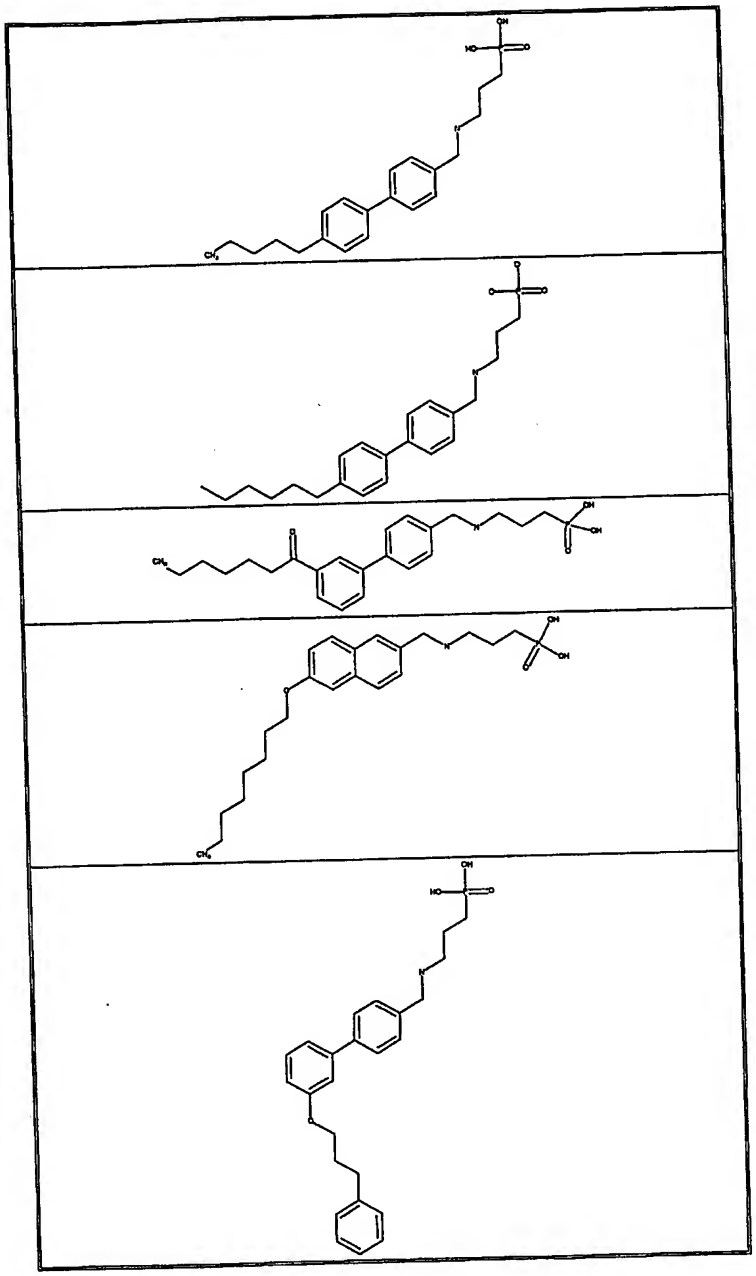


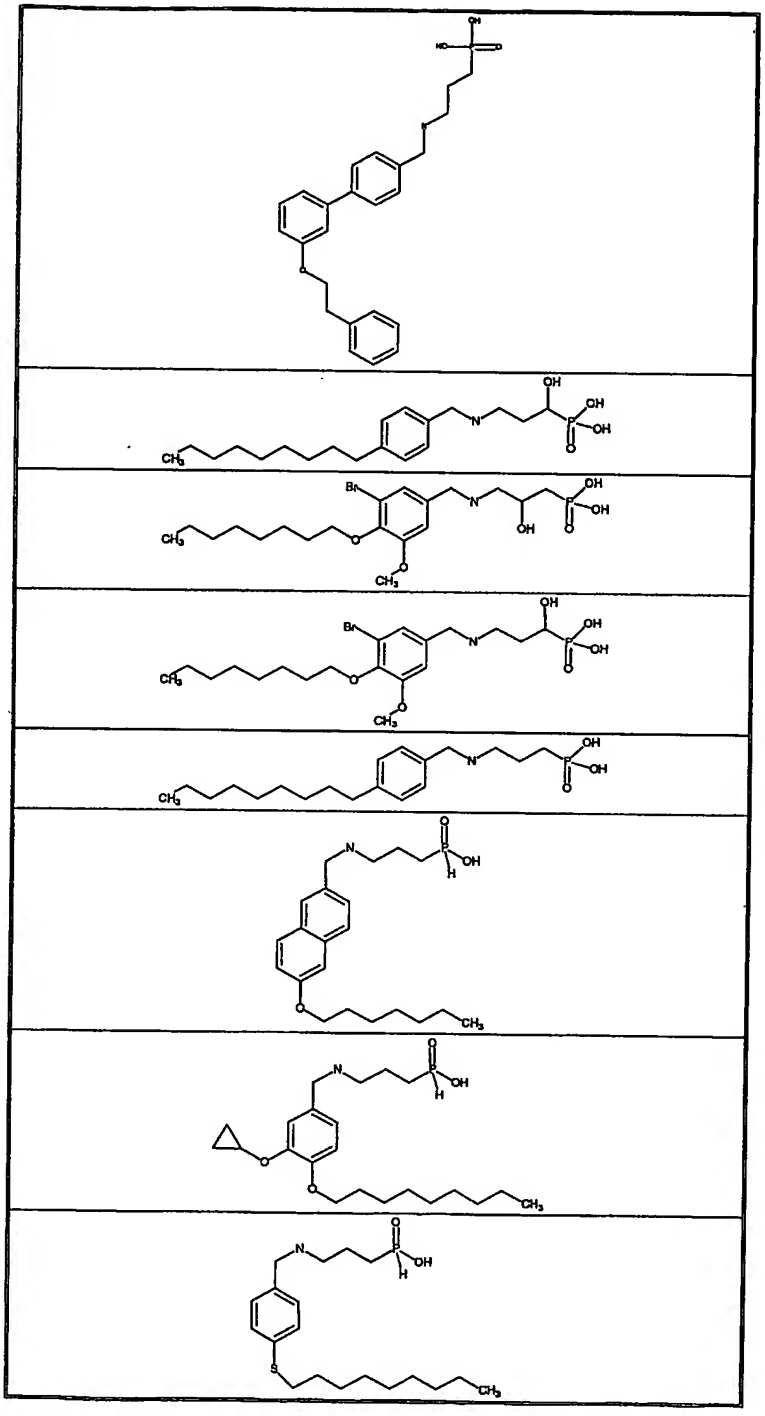


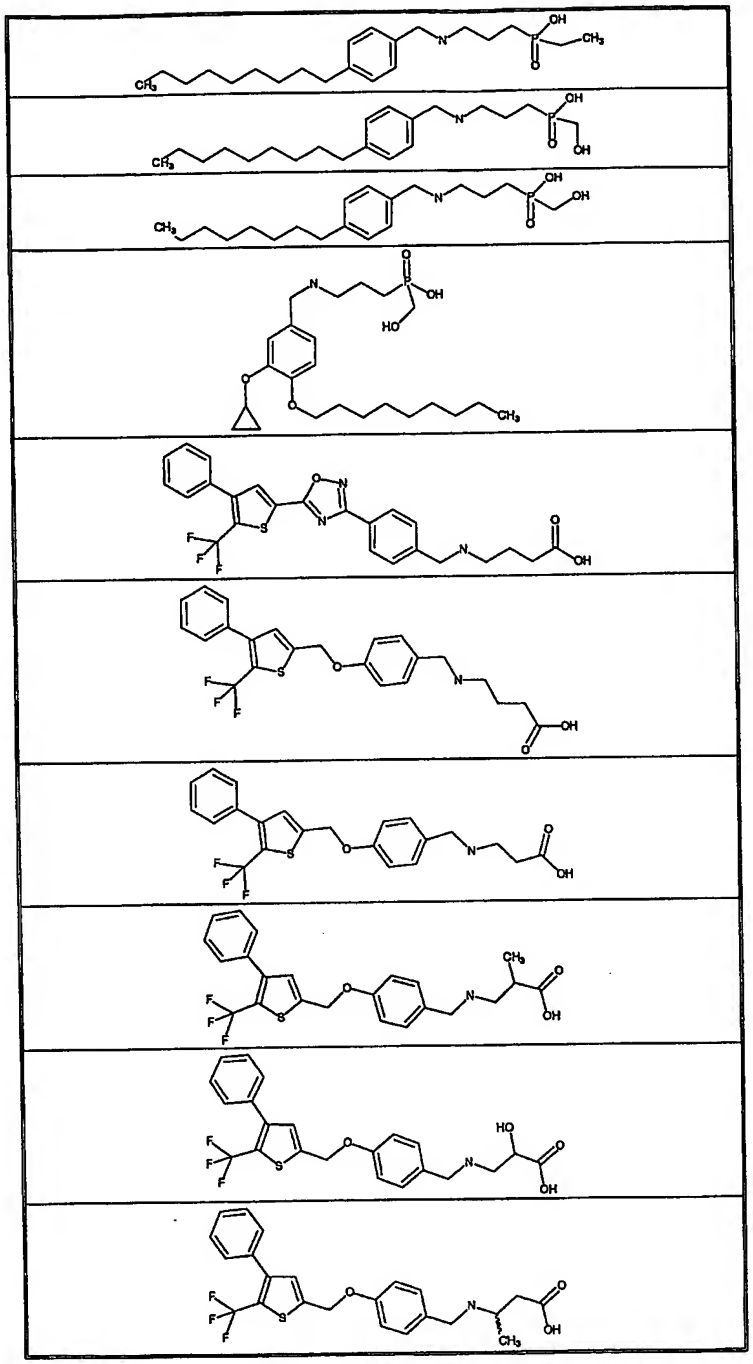












The present invention also includes a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and the compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof. A preferred embodiment of the formulation is one where a second immunosuppressive agent is also included. Examples of such second immunosuppressive agents are, but are not limited to azathioprine, brequinar sodium, deoxyspergualin, mizaribine, mycophenolic acid morpholino ester, cyclosporin, FK-506, rapamycin and FTY720.

The present compounds, including salts and hydrates thereof, are useful in the treatment of autoimmune diseases, including the prevention of rejection of bone marrow transplant, foreign organ transplants and/or related afflictions, diseases and illnesses.

The compounds of this invention can be administered by any means that effects contact of the active ingredient compound with the site of action in the body of a warm-blooded animal. For example, administration, can be oral, topical, including transdermal, ocular, buccal, intranasal, inhalation, intravaginal, rectal, intracisternal and parenteral. The term "parenteral" as used herein refers to modes of administration which include subcutaneous, intravenous, intramuscular, intraarticular injection or infusion, intrasternal and intraperitoneal.

The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will be dependent on the age, health and weight of the recipient, the extent of disease, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. Usually, a daily dosage of active ingredient compound will be from about 0.1-2000 milligrams per day. Ordinarily, from 1 to 100 milligrams per day in one or more applications is effective to obtain desired results. These dosages are the effective amounts for the treatment of autoimmune diseases, the prevention of rejection of foreign organ transplants and/or related afflictions, diseases and illnesses.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The active ingredient can also be administered parenterally, in sterile liquid dosage forms, such

as dispersions, suspensions or solutions. Other dosages forms that can also be used to administer the active ingredient as an ointment, cream, drops, transdermal patch or powder for topical administration, as an ophthalmic solution or suspension formation, i.e., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene gycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field.

For administration by inhalation, the compounds of the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons.

For ocular administration, an ophthalmic preparation may be formulated with an appropriate weight percent solution or suspension of the compounds of Formula I in an appropriate ophthalmic vehicle, such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

CAPSULES

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

SOFT GELATIN CAPSULES

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

TABLETS

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

INJECTABLE

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

SUSPENSION

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

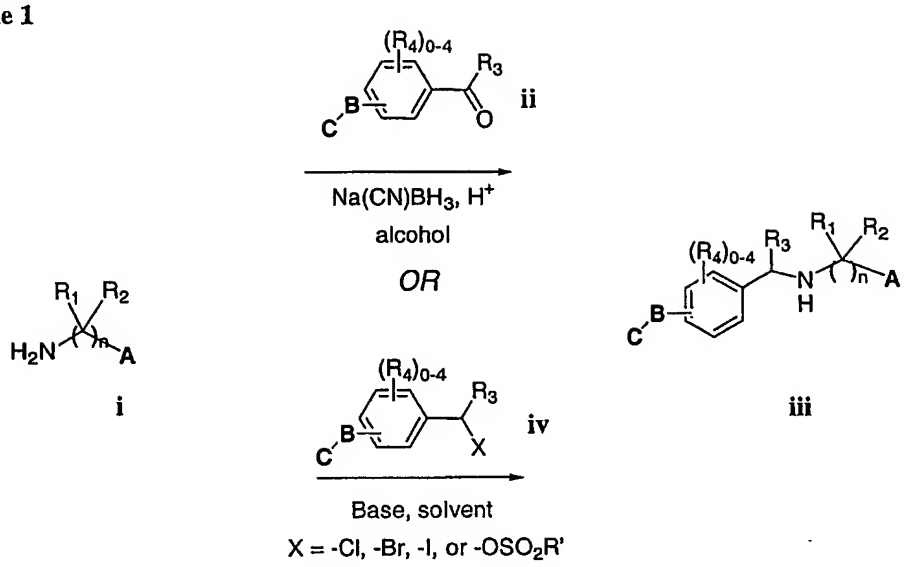
The same dosage forms can generally be used when the compounds of this invention are administered stepwise or in conjunction with another therapeutic agent. When drugs are administered in physical combination, the dosage form and

administration route should be selected depending on the compatibility of the combined drugs. Thus the term coadministration is understood to include the administration of the two agents concomitantly or sequentially, or alternatively as a fixed dose combination of the two active components.

METHODS OF SYNTHESIS

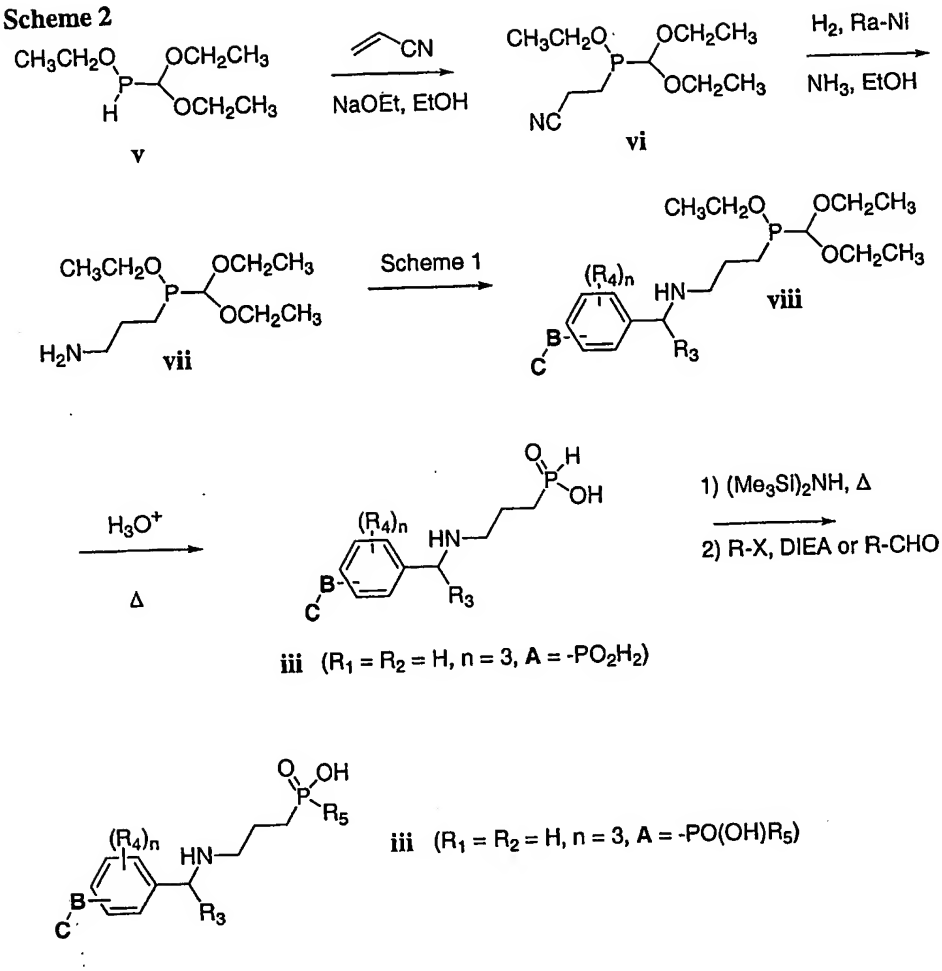
Two general methods that can be employed to prepare compounds in the current invention are depicted in Scheme 1. Intermediates **i** are in many cases available from commercial sources (e.g., β-alanine, where A = $-CO_2H$, R_1 = H, R_2 = H, n = 2; 4-(amino)butanoic acid, where A = $-CO_2H$, R_1 = H, R_2 = H, n = 3; 3-(amino)propyl phosphonic acid, where A = $-PO_3H_2$, R_1 = H, R_2 = H, n = 3). Intermediates **i** can also be prepared using methods known to those skilled in the art or using methods described below. Combining **i** with an aryl aldehyde **ii** in the presence of an appropriate reducing agent (e.g., sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride) in a compatible solvent (e.g., methanol, ethanol, acetonitrile, methylene chloride) can afford compounds of structure **iii**. Alternatively, intermediates **i** can be combined with a benzyl halide or sulfonate ester **iv** in the presence of an appropriate base (e.g., sodium carbonate, potassium carbonate, triethylamine, N,N-diisopropylethylamine) in a compatible solvent solvent (e.g., methanol, ethanol, acetonitrile) at or above room temperature to give compounds of structure **iii**. In cases where A in structure **i** would interfere with the transformation to **iii**, an appropriate protecting group (Greene & Wuts, eds., "Protecting Groups in Organic Synthesis", John Wiley & Sons, Inc.) that would mask A and allow for the liberation of A after coupling with either **ii** or **iv** can be employed. In cases where **iii** contains asymmetric centers, the individual stereoisomers of **iii** can obtained by methods known to those skilled in the art which include (but are not limited to): stereospecific synthesis, resolution of salts of **iii** or any of the intermediates used in its preparation with enantiopure acids or bases, resolution of **iii** or any of the intermediates used in its preparation by HPLC employing enantiopure stationary phases.

Scheme 1



Methods to prepare analogs **iii** in which R_1 = H, R_2 = H, n = 3 and **A** = $-PO_2H_2$ and R_1 = H, R_2 = H, n = 3 and **A** = $-PO(OH)R_5$ are shown in Scheme 2. Ethyl diethoxymethylphosphinic acid (**v**) can be treated with acrylonitrile in the presence of a base (e.g., sodium hydride, sodium ethoxide, lithium diisopropylamide) in a suitable solvent (e.g., EtOH, THF) at or below room temperature to afford **vi**. Reduction of the cyano group of **vi** using catalytic hydrogenation affords **vii** which can be converted to **viii** using the methods described in Scheme 1 to convert **i** to **iii**. Treating **viii** with strong aqueous acid at or above room temperature can give **iii** in which R_1 = H, R_2 = H, n = 3 and **A** = $-PO_2H_2$. Phosphinic acid alkylation can be carried out by conversion of the phosphinic acid to the bis(trimethylsilyl) ester and treating it with an electrophile (e.g., an alkyl halide, an alkyl or aryl aldehyde) to give the alkylated product (R_1 = H, R_2 = H, n = 3 and **A** = $-PO(OH)R_5$).

Scheme 2



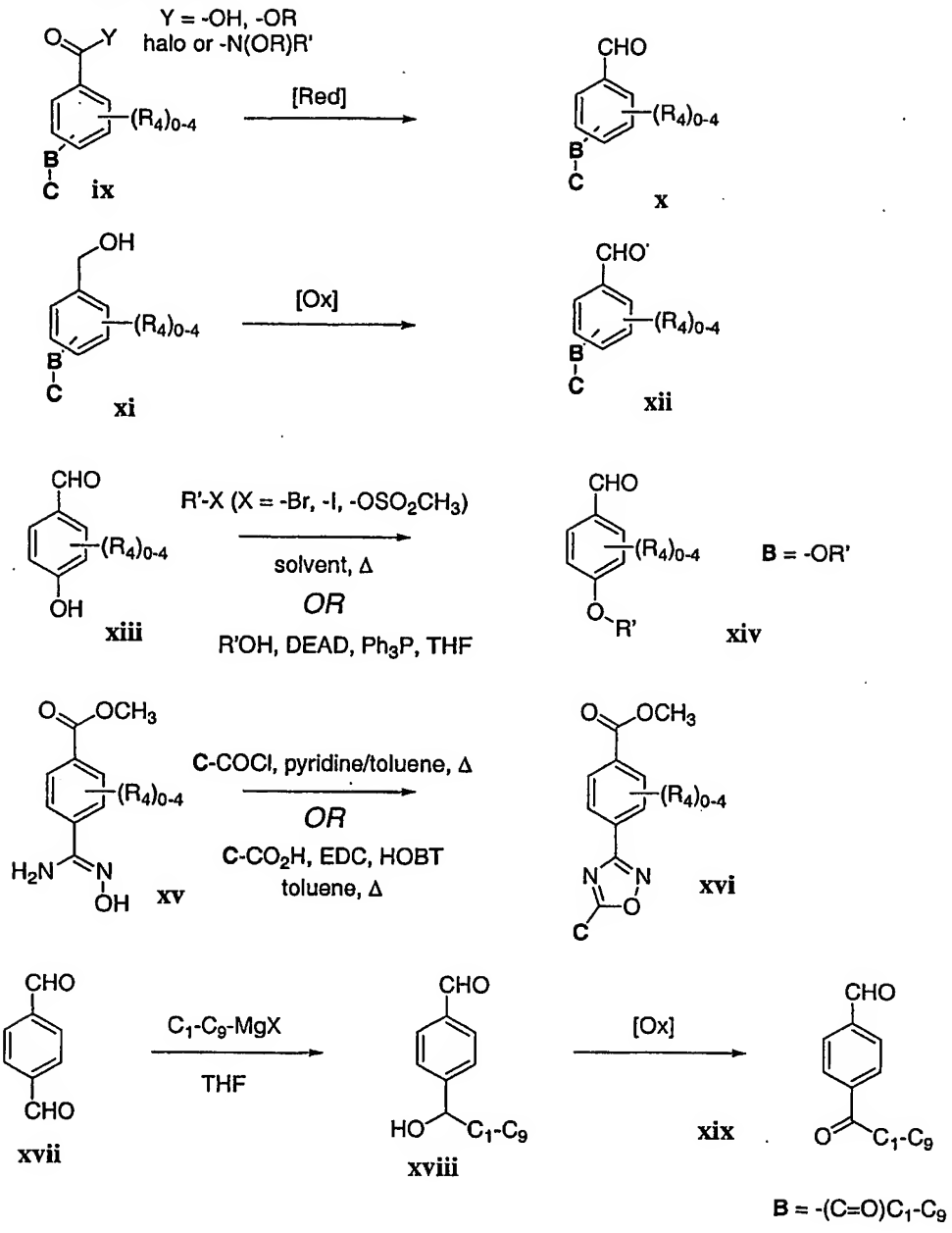
iii ($R_1 = R_2 = H$, n = 3, **A** = $-PO_2H_2$)

iii ($R_1 = R_2 = H$, n = 3, **A** = $-PO(OH)R_5$)

Several methods that can be used to prepare compounds that can be employed as intermediate **ii** in Scheme 1 above are shown in Scheme 3. Many aryl carboxylic acids, aryl carboxylic acid halides, aryl carboxylic esters, and aryl N-alkoxyl-N-alkyl carboxamides (**ix**) are commercially available and can be converted to aryl aldehydes (**x**) using reduction methods known by those skilled in the art (see Larock, "Comprehensive Organic Transformations, A Guide to Functional Group Preparations", VCH Publishers, Inc.). Alternatively, many benzyl alcohols (**xi**) are commercially available and can be converted to aryl aldehydes (**xii**) using oxidation methods known by those skilled in the art. For cases where **B** = alkoxy, a hydroxy

benzaldehyde **xiii** can be combined with a alkyl halide or sulfonate ester in the presence of an appropriate base (e.g., sodium hydride, sodium carbonate, potassium carbonate, triethylamine, N,N-diisopropylethylamine) in a compatible solvent solvent (e.g., DMF, methanol, ethanol, acetonitrile) at or above room temperature to give compounds of structure **xiv**. Alternatively, a hydroxy benzaldehyde **xiii** can be combined with an alcohol, a dialkyl azodicarboxylate (e.g., diethyl azodicarboxylate, diisopropylazodicarboxylate) and triphenylphosphene in an appropriate solvent (THF, toluene, methylene chloride) to give **xiv**. For cases where **B** is 1,2,4-oxadiazolyl, N-hydroxyamidine **xv** can be treated with an acid chloride in an appropriate solvent (xylenes, toluene) in the presence of an amine base (pyridine, DBU) with heating to give an intermediate **xvi**. Alternatively, **xv** can be treated with a carboxylic acid, a carbodiimide (e.g., N,N'-dicyclohexylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide) and 1-hydroxybenzotriazole in an appropriate solvent (xylenes, toluene) to give **xvi**. Prepared by either manner, the ester group of **xv** can be converted to aldehyde with methods employed to convert **ix** to **x**. For cases where **B** is $-(C=O)C_{6\text{-}11}$ alkyl and R_4 = H, an aryl 1,4-dialdehyde (**xvii**) can be treated with a limiting amount of an alkyl organometallic reagent (e.g., alkyl magnesium bromide, alkyl lithium) at or below room temperature in an ethereal solvent (e.g., THF, diethyl ether, 1,2-dimethoxyethane) to afford intermediate **xviii**. Mild oxidation of **xviii** (e.g., treatment with oxalyl chloride and DMSO at – 78 °C in dichloromethane

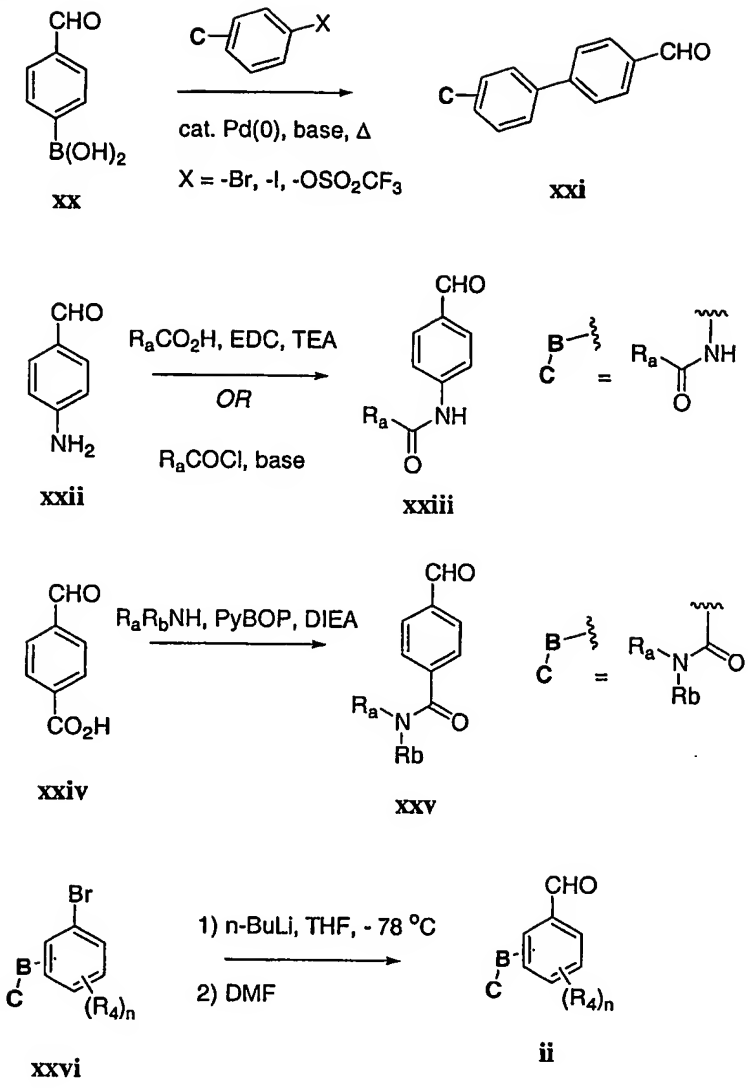
Scheme 3


Y = -OH, -OR
halo or -N(OR)R'
[Red]
[Ox]
R'-X (X = -Br, -I, -OSO2CH3)
solvent, Δ
OR
R'OH, DEAD, Ph3P, THF
B = -OR'
C-COCl, pyridine/toluene, Δ
OR
C-CO2H, EDC, HOBT
toluene, Δ
C1-C9-MgX
THF
[Ox]
B = -(C=O)C1-C9

followed by a trialkylamine base and warming (Swern oxidation); treatment with 4-methylmorpholine N-oxide and catalytic tetrapropylammonium peruthenate in acetonitrile; Dess-Martin reagent in methylene chloride) can give aldehyde **xix**.

Several other methods that can be used to prepare compounds that can be employed as intermediate **ii** in Scheme 1 above are shown in Scheme 4. For intermediates in which **B** = phenyl and R_4 = H, 4-(formyl)phenyl boronic acid (**xx**) can by reacted with an aryl bromide, iodide or trifluoromethanesulfonate ester in the presence of a palladium catalyst (e.g., tetrakis(triphenylphosphine)palladium, 2-(dicyclohexylphosphino)biphenyl and palladium acetate) in the presence of an appropriate base (e.g., potassium carbonate, potassium fluoride) in an appropriate solvent (e.g., ethanol, 1,4-dioxane, THF) at or above room temperature to give **xxi**. Intermediates in which the phenyl ring is substituted with an amide linkage (either **xxiii** or **xxv**) can be prepared by methods known by those skilled in the art to prepare amides from carboxylic acid derivatives (see Larock, "Comprehensive Organic Transformations, A Guide to Functional Group Preparations", VCH Publishers, Inc.). Additionally, **ii** can be prepared by treating an aryl bromide (**xxvi**) with an alkyl lithium (e.g., n-butyllithium, t-butyllithium) in a compatible solvent (e.g., diethyl ether, 1,2-dimethoxyethane, THF) at or below room temperature followed by reacting the formed aryl lithium with N,N-dimethylformamide to give **ii**.

Scheme 4


CHO
B(OH)2
xx
C
X
cat. Pd(0), base, Δ
X = -Br, -I, -OSO2CF3
CHO
C
xxi
CHO
NH2
xxii
RaCO2H, EDC, TEA
OR
RaCOCl, base
CHO
Ra
NH
O
xxiii
B
C
=
Ra
NH
O
CHO
CO2H
xxiv
RaRbNH, PyBOP, DIEA
CHO
Ra
N
Rb
O
xxv
B
C
=
Ra
N
Rb
O
Br
B
C
(R4)n
xxvi
1) n-BuLi, THF, - 78 °C
2) DMF
CHO
B
C
(R4)n
ii

Methods for preparing the compounds of this invention are further illustrated in the following examples. Alternative routes will be easily discernible to practitioners in the field.

GENERAL METHODS

Concentration of solutions was carried out on a rotary evaporator under reduced pressure. Conventional flash chromatography was carried out on silica gel (230-400 mesh). Flash chromatography was also carried out using a Biotage Flash Chromatography apparatus (Dyax Corp.) on silica gel (32-63 mM, 60 Å pore size) in pre-packed cartridges of the size noted. NMR spectra were obtained in $CDCl_3$ unless otherwise noted. Coupling constants (J) are in hertz (Hz). Abbreviations: diethyl ether (ether), triethylamine (TEA), N,N-diisopropylethylamine (DIEA), tetrahydrofuran (THF), saturated (sat'd), room temperature (rt), hour(s) (h or hr), min(s) (min). For all tables that follow any NMR data follows the compound.

HPLC METHODS

LC-1: Waters Xterra MS C18, 5 μ, 4.6 x 50 mm column, 10:90 to 95:5 v/v CH_3CN/H_2O + 0.05% TFA over 4.5 min, hold 1 min, PDA detection 200-600 nm, flow rate = 2.5 mL/min.

LC-2: Analytical Sales and Service Armor C8 5 μ 20 x 100 mm column, 10:90 to 90:10 v/v CH_3CN/H_2O + 0.05% TFA over 12 min, hold 4 min, UV detection at either 210, 220 or 254 nM, flow rate = 10 mL/min.

LC-3: YMC-Pack Pro C18, 5μ, 20 mm x 150 mm column, gradient 10:90-80:20 v/v $CH_3CN:H_2O$ + 0.1% TFA over 23 min then hold at 100:0 v/v $CH_3CN:H_2O$ + 0.1% TFA for 7 min; 20 mL/min, 254 nm.

PREPARATION OF ALDEHYDE INTERMEDIATES

Aldehyde 1

4-Octyloxybenzaldehyde

4-Hydroxybenzaldehyde (1.00 g, 0.82 mmol), potassium carbonate (1.70 g, 12.28 mmol) and 1-iodooctane (2.16 g, 9.00 mmol) were heated together in acetonitrile at 80°C for 16 h. The reaction was cooled, filtered and concentrated.

Silica gel chromatography eluting with hexane/ethyl acetate (20:1) gave a colorless oil (1.63 g): ^{1}H NMR (500 MHz) δ 9.99 (s, 1H), 7.44-7.46 (m, 2H), 7.40 (s, 1H), 7.19 (m, 1H), 4.01 (t, J=6.6 Hz, 2H), 1.80 (m, 2H), 1.42-1.50 (m, 2H), 1.24-1.39 (m, 8H), 0.89 (t, J=6.9 Hz, 3H).

Aldehyde 2

4-Hydroxy-3-propyloxybenzaldehyde

3,4-Dihydroxybenzaldehyde (0.5 g, 3.62 mmol) was dissolved in DMF (10 mL) and sodium hydride (0.087 g, 3.62 mmol) was added. The reaction mixture was stirred at rt for 10 min. Iodopropane (0.35 mL, 0.62 mmol) was added and the reaction was stirred at 80 °C for 2.5 h. The reaction was diluted with ethyl acetate and washed with 2N HCl and water. Silica gel chromatography eluting with 35% ethyl acetate/hexane yielded 0.16 g of desired product: ESI-MS 181 (M+H).

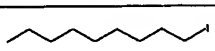
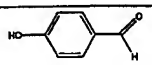
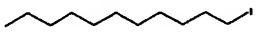
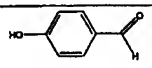
Aldehyde 3

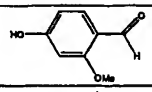
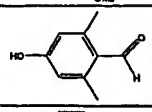
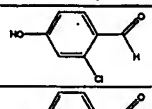
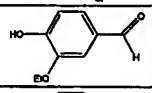
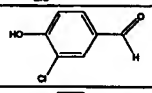
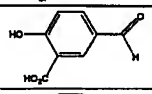
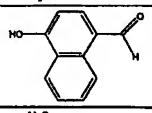
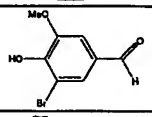
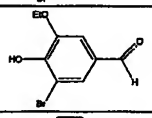
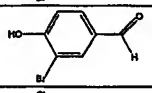
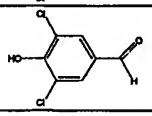
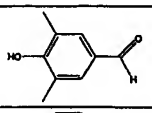
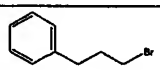
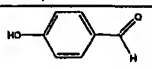
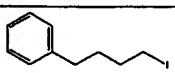
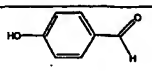
6-Hydroxy-2-naphthaldehyde

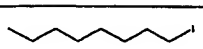
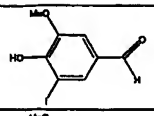
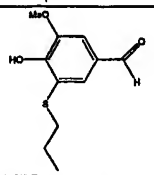
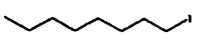
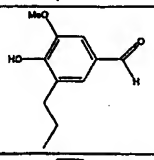
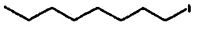
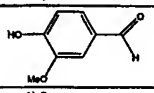
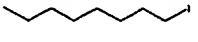
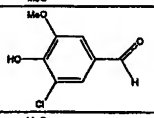
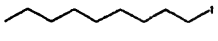
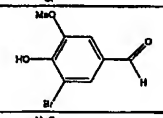
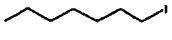
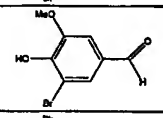
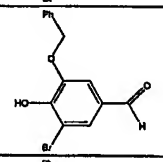
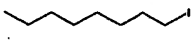
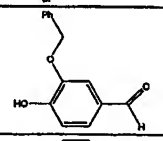
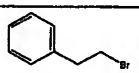
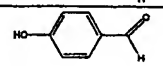
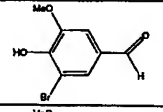
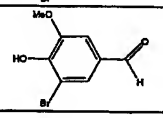
Aluminum trichloride (1.07 g, 8.06 mmol) was added to a solution of 6-methoxy-2-naphthaldehyde (1.0 g, 5.37 mmol) in chlorobenzene (15 mL). The reaction mixture was stirred at 130 °C for 4 h. The reaction was quenched with water (5 mL) and conc. HCl (2 mL). The reaction mixture was dissolved in ethyl acetate and washed with water and brine and dried over anhydrous magnesium sulfate. Silica gel chromatography eluting with 10% ethyl acetate/hexane yielded 0.35 g of desired product: ESI-MS173.0 (M+H).

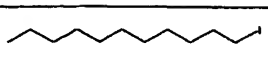
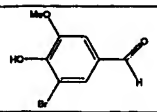
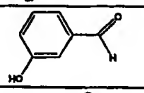
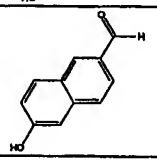
Aldehydes 4-34

The following Aldehydes (4-34) were prepared using a procedure analogous to that described for Aldehyde 1 substituting A for 1-iodooctane and B for 4-hydroxybenzaldehyde.

Aldehyde	A	B	ESI-MS
4			249.3
5			277.1

6			265.4
7			263.1
8			269.0
9			279.1
10			
11			262.0
12			
13			343.0
14			357.1
15			
16			
^{1}H NMR (500 MHz, CD_3OD) δ 9.88 (s, 1H), 7.94 (s, 1H), 7.47 (s, 1H), 4.26 (t, J=6.3 Hz, 2H), 4.14 (t, J=6.3 Hz, 2H), 4.02 (t, J=6.3 Hz, 2H), 3.25 (t, J=6.8 Hz, 2H), 1.76-1.94 (m, 4H), 1.52-1.62 (m, 2H), 0.88-1.00 (m, 3H)			
17			
18			241.1
19			255.2

20			391.1
21			339.3
22			307.3
23			265.2
24			299.1
25			357.1
26			329.0
27			419.1
28			341.3
29			227.1
30			370.9
31			317.1

32			382.7
33			179.1
34			285.1

Aldehyde 35

3-Methoxy-5-methyl-4-octyloxybenzaldehyde

Aldehyde 20 (0.20 g, 0.51 mmol) and tetramethyl tin (0.2 g, 1.12 mmol) were dissolved in N-methyl pyrrolidinone (1 mL) in a sealed tube. Palladium tetrakis(triphenylphosphine) (0.016 g, 0.014 mmol) and copper iodide (0.01 g, 0.05 mmol) were added to the reaction mixture which was heated at 65° for 16 h. The reaction mixture was diluted with ethyl acetate and washed with 2N HCl, brine and was dried over magnesium sulfate. Silica gel chromatography eluting with 10% ethyl acetate/hexane gave desired product: ESI-MS 279.2 (M+H).

Aldehyde 36

3-Methoxy-5-phenyl-4-octyloxybenzaldehyde

Aldehyde 20 (0.25 g, 0.64 mmol), phenylboronic acid (0.12 g, 0.96 mmol), potassium carbonate (0.27 g, 1.92 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.15 g, 0.016 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.022 g, 0.064 mmol) were dissolved in tetrahydrofuran (1 mL). The reaction mixture was stirred at rt for 3 h then at 50 °C for 16 h. The reaction mixture was filtered through celite. Silica gel chromatography eluting with 10% ethyl acetate/hexane gave desired product: ESI-MS 341.2 (M+H).

Aldehyde 37

3-Hydroxy-4-octyloxybenzaldehyde

Aldehyde 28 (0.25 g, 0.77 mmol) was dissolved in methylene chloride (4 mL) and boron tribromide dimethylsulfide complex (0.6 g, 1.93 mmol) was added dropwise. The reaction mixture was stirred at rt for 1 h. The reaction was quenched

with methanol and concentrated *in vacuo*. Silica gel chromatography eluting with 10% ethyl acetate/hexane yielded 0.155 g of desired product: ESI-MS 251.2 (M+H).

Aldehyde 38

4-(Nonoylamido)benzaldehyde

4-Aminobenzaldehyde (0.3 g, 2.5 mmol) was dissolved in methylene chloride (8 mL) and nonanoyl chloride (0.5 mL, 2.7 mmol) was added followed by DIEA (1.14 mL, 6.25 mmol). The reaction was stirred at rt for 3 h. Silica gel chromatography eluting with 25% ethyl acetate/hexane yielded impure product Further purified by HPLC to give 30.0 mg of desired product: ESI-MS 262.0 (M+H).

Aldehyde 39

4-(5-Phenylpentyloxy)benzaldehyde

Diethylazodicarboxylate (0.49 g, 2.8 mmol) in tetrahydrofuran (2 mL) was added to a solution of 4-hydroxybenzaldehyde (0.25 g, 2.05 mmol), 5-phenyl-1-pentanol (0.34 mL, 2.05 mmol) and triphenylphosphine (0.73 g, 2.80 mmol) in tetrahydrofuran (10 mL) at rt. The reaction was stirred for 2h. The reaction mixture was concentrated *in vacuo*. Silica gel chromatography eluting with 20% ethyl acetate/hexane yielded 0.070 g of desired product: ^{1}H NMR (500 MHz , CD_3OD): δ 9.83 (s, 1H), 7.86 (d, J=8.7 Hz, 2H), 7.25 (t, 2H), 7.14-7.20 (m, 3H), 7.06 (d, J=8.7 Hz, 2H), 4.09 (t, J=6.4 Hz, 2H), 2.65 (t, J=7.7 Hz, 2H), 1.80-1.88 (m, 2H), 1.68-1.75 (m, 2H), 1.49-1.57 (m, 2H).

Aldehyde 40

3'-Chloro-4'-octyloxy-4-biphenylbenzaldehyde

Step A: 1-Bromo-3-chloro-4-octyloxybenzene

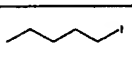
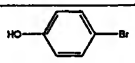
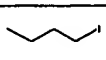
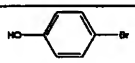
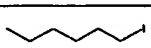
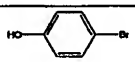
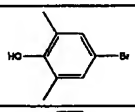
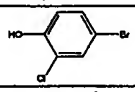
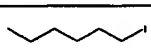
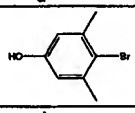
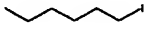
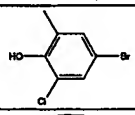
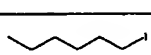
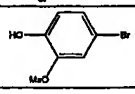
1-Bromo-3-chloro-4-hydroxybenzene (0.50 g, 2.41 mmol) was dissolved in acetonitrile (20 mL) and stirred at rt. Potassium carbonate (0.47 g, 3.37 mmol) and iodooctane (0.57 mL, 3.13 mmol) were added and the reaction was heated to 80 °C for 4 h. The reaction was diluted with ethyl acetate, washed with water and dried over anhydrous magnesium sulfate. Silica gel chromatography eluting with 1% ethyl acetate/hexane yielded 0.6 g of product: ESI-MS 317.0 (M+H).

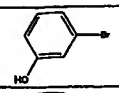
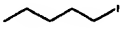
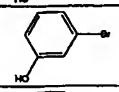
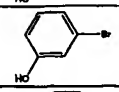
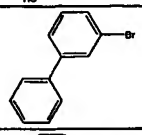
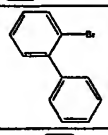
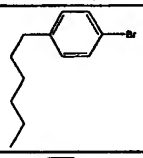
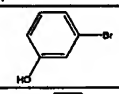
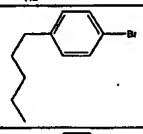
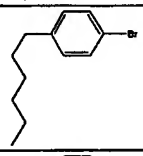
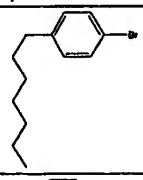
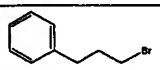
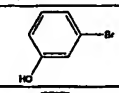
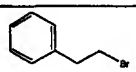
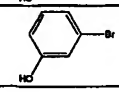
Step B: 3'-Chloro-4'-octyloxy-4-biphenylbenzaldehyde

Palladium acetate (0.005 g, 0.022 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.015 g, 0.044 mmol) were added to a solution of (4-formylphenyl)boronic acid (0.25 g, 1.65 mmol), 1-bromo-3-chloro-4-octoxybenzene (0.35 g, 1.10 mmol, from Step A), and potassium fluoride (0.19 g, 3.30 mmol) in 1,4-dioxane (3 mL). The reaction mixture was heated at 75 °C for 3 h. The reaction was cooled, filtered through celite and concentrated *in vacuo*. Silica gel chromatography eluting with 1% ethyl acetate/hexane yielded 0.17 g of desired product: ^{1}H NMR (500 MHz , CD_3OD): δ 10.01 (s, 1H), 7.97 (d, J=8.0 Hz, 2H), 7.80 (d, J=8.0 Hz, 2H), 7.74 (s, 1H), 7.61 (d, J=7.7 Hz, 1H), 7.16 (d, J=8.7 Hz, 1H) 4.11 (t, J=6.2 Hz, 2H), 1.80-1.89 (m, 2H), 1.50-1.60 (m, 2H), 1.28-1.46 (m, 8H), 0.88-0.97 (m, 3H)

Aldehydes 41-60

The following Aldehydes (41-60) were made using procedures analogous to those described for Aldehyde 40 substituting A for 1-iodooctane and B for 1-bromo-3-chloro-4-hydroxybenzene in Step A

Aldehyde	A	B	ESI-MS
41			269.1
42			255.0
43			283.1
44			311.0
45			
46			311.3
47			331.1
48			313.2

49			255.1
50			269.2
51			
52	N/A		259.0
53	N/A		259.0
54	N/A		267.1
55			297.1
56	N/A		253.2
57	N/A		267.1
58	N/A		
59			
60			

Aldehyde 61

4-(Octyloxymethyl)benzaldehyde

Step A: 4-(Octyloxymethyl)benzyl alcohol

Sodium hydride (0.17 g, 7.20 mmol) was added to a solution of 1,4-benzene dimethanol (1.00 g, 7.20 mmol) in THF at 0 °C. The reaction was stirred for 1 h. 1-iodooctane (1.73 g; 7.20 mmol) was added and the reaction mixture was warmed to rt for 4 h and then heated at 50°C for 2 days. The reaction was cooled and filtered. Silica gel chromatography eluting with 15% ethyl acetate/hexane gave 0.14 g of product: ^{1}H NMR (500 MHz) δ 7.34-7.40 (m, 4H), 4.68-4.72 (m, 2H), 4.51 (s, 2H), 3.46-3.50 (m, 2H), 1.61-1.68 (m, 2H), 1.24-1.40 (m, 10H), 0.88-0.92 (m, 3H).

Step B: 4-(Octyloxymethyl)benzaldehyde

4-(Octyloxymethyl)benzyl alcohol (0.14 g, 0.56 mmol, from Step A) was dissolved in methylene chloride (1.5 mL) and the reaction mixture was cooled to 0 °C. 4-methylmorpholine N-oxide (0.10 g, 0.84 mmol) and molecular sieves (4A) (0.25 g) were added. Tetrapropylammonium perruthenate (0.004 g, 0.011 mmol) was added and the resulting mixture was stirred for 1 h. The reaction mixture was filtered through celite. Silica gel chromatography eluting with 6% ethyl acetate/hexane gave 0.018 g of product: ^{1}H NMR (500 MHz) δ 10.02 (s, 1H), 7.86-7.90 (m, 2H), 7.50-7.55 (m, 2H), 4.58-4.62 (s, 2H), 3.50-3.55 (m, 2H), 1.62-1.70 (m, 2H), 1.24-1.35 (m, 2H), 0.87-0.93 (m, 2H).

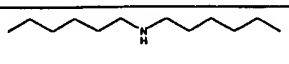
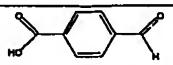
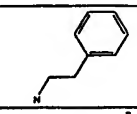
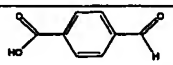
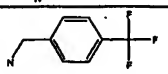
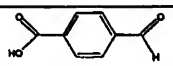
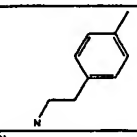
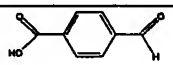
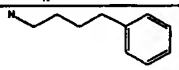
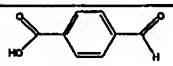
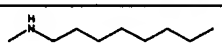
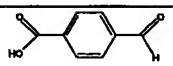
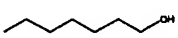
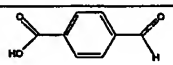
Aldehyde 62

4-(N-Octylcarboxamido)benzaldehyde

DIEA (0.43 mL, 2.33 mmol) was added to a solution of 4-carboxybenzaldehyde (0.23 g, 1.55 mmol), octylamine (0.20 g, 1.55 mmol) and PyBoP (0.89 g, 1.71 mmol) in methylene chloride (2.5 mL). The reaction was stirred at rt for 16 h after which it was concentrated. Silica gel chromatography eluting with 25% ethyl acetate/hexane gave 0.30 g of product: ESI-MS 262.1 (M+H).

Aldehydes 63-73

The following Aldehydes (63-73) were made using a procedure analogous to that described for Aldehyde 62 substituting A for octylamine.

Aldehyde	A	B	ESI-MS
63			318.2
64			253.0
65			
66			282.2
67			282.2
68			
69			
^{1}H NMR (500 MHz): δ 10.10 (s, 1H), 8.20 (d, J=8.2 Hz, 2H), 7.95 (d, J=8.2 Hz, 2H), 4.35 (t, J=6.8 Hz, 2H), 1.75-1.85 (m, 2H), 1.40-1.50 (m, 2H), 1.25-1.40 (m, 6H), 0.89 (t, J=7.0 Hz, 3H).			

Aldehyde 70

4-(1-Hydroxynon-1-yl)benzaldehyde

Terephthaldicarboxaldehyde (2.00 g, 14.91 mmol) was dissolved in tetrahydrofuran (25 mL) and cooled to 0°C. Octylmagnesium chloride (7.5 mL, 2.0M in THF, 15 mmol) was added dropwise. After 15 min, the reaction was quenched with 2N aqueous hydrochloric acid (50 mL) and diluted with ethyl acetate (50 mL). The organic layer was separated, washed with sat'd sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 9% ethyl acetate/hexane gave 0.19 g (0.77 mmol, 5.1%) of product: ^{1}H NMR (500 MHz) δ 10.0 (s, 1H), 7.87 (d, J=8.0 Hz, 2H), 7.52 (d, J=8.3 Hz, 2H), 4.75-4.80 (m, 1H), 1.68-1.82 (m, 2H), 1.22-1.45 (m, 12H), 0.91 (t, J=7.0 Hz, 3H).

Aldehyde 71

4-(1-Nonoyl)benzaldehyde

Dess-Martin periodinane (0.268 g, 0.632 mmol) was added to a solution of Aldehyde 70 (0.125 g, 0.505 mmol) in methylene chloride (3.0 mL). After 1 h, the reaction was filtered and concentrated in vacuo. Silica gel chromatography eluting with 5% ethyl acetate/hexane gave 0.107 g (0.446 mmol, 88%) of product: ^{1}H NMR (500 MHz) δ 10.1 (s, 1H), 8.10 (d, J=8.2 Hz, 2H), 7.97 (d, J=8.2 Hz, 2H), 3.00 (t, J= 7.3 Hz, 2H), 1.70-1.8 (m, 2H), 1.22-1.42 (m, 10H), 0.88 (t, J=7.0 Hz, 3H).

Aldehyde 72

4-(1-Decanoyl)benzaldehyde

Tetrakis(triphenylphosphine)palladium(0) (50 mg) was added to a solution of 4-formylphenylboronic acid (0.50 g, 3.33 mmol), nonanoyl chloride (1.7 mL, 8.33 mmol) and cesium carbonate (2.70 g, 8.33 mmol) in toluene (40 mL) and heated to 80 °C. After stirring overnight, the reaction was diluted with ethyl acetate (50 mL) and washed with 2N hydrochloric acid (50 mL), sat'd sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 6% ethyl acetate/hexane gave 0.022 g (0.083 mmol, 3%) of product: ^{1}H NMR (500 MHz) δ 10.1 (s, 1H), 8.09 (d, J=8.2 Hz, 2H), 7.98 (d, J=8.2 Hz, 2H), 3.00 (t, J= 7.4 Hz, 2H), 1.70-1.80 (m, 2H), 1.22-1.42 (m, 12H), 0.88 (t, J=6.9 Hz, 3H).

Aldehyde 73

3-Methyl-4-decanoyl benzaldehyde

Step A: 4-Bromo-3-methylbenzyl alcohol

DIBALH (1.0M solution in methylene chloride, 31 mL, 31 mmol) was added dropwise to a solution of methyl 4-bromo-3-methylbenzoate (3.0 g, 14.0 mmol) in methylene chloride (20 mL) at 0 °C. After 1 h, the reaction was quenched with 10% aqueous sodium bisulfite (100 mL). The aqueous layer was separated and extracted with methylene chloride (50 mL). The combined organic layers were combined, dried over magnesium sulfate and concentrated in *vacuo*. Silica gel chromatography eluting with 17% ethyl acetate/hexane gave 1.90 g (9.50 mmol, 68%) of product: ^{1}H NMR (500 MHz) δ 7.50 (d, J=8.3 Hz, 1H), 7.24 (s, 1H), 7.04 (d, J=8.0 Hz, 1H), 4.62 (d, J= 5.7 Hz, 2H), 2.40 (s, 3H).

Step B: 4-(1-Hydroxydec-1-yl)-3-methylbenzyl alcohol

n-Butyllithium (2.5 M in hexanes, 8.3 mL, 20.7 mmol) was added dropwise to a solution of 4-bromo-3-methylbenzyl alcohol (1.90 g, 9.44 mmol, from Step A) in tetrahydrofuran (25 mL) at –78 °C. After 1 h, n-decanal (2.95 g, 18.89 mmol) was added and the reaction allowed to warm to 0°C. After 30 min, the reaction was quenched with water (25 mL) and diluted with ethyl acetate (25 mL). The organic layer was washed with sat'd sodium chloride (30 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 25% ethyl acetate/hexane gave 1.69 g (6.07 mmol, 64%) of product: ^{1}H NMR (500 MHz): δ 7.45 (d, J=8.0 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 7.14 (s, 1H), 4.88-4.94 (m, 1H), 4.64 (s, 2H), 2.34 (s, 3H), 1.22-1.80 (m, 16H), 0.87 (t, J=7.0 Hz, 3H).

Step C: 3-Methyl-4-decanoyl benzaldehyde

Dess-Martin periodinane (1.00 g, 2.37 mmol) was added to a solution of 4-(1-hydroxydec-1-yl)-3-methylbenzyl alcohol (0.300 g, 1.07 mmol, from Step B) in methylene chloride (5.0 mL). After 20 min, the reaction was filtered and concentrated *in vacuo*. Silica gel chromatography eluting with 5% ethyl acetate/hexane gave 0.24 g (0.89 mmol, 83%) of product: ^{1}H NMR (500 MHz) δ 10.0 (s, 1H), 7.76 (d, J=7.8 Hz, 1H), 7.74 (s, 1H), 7.66 (d, J=7.8 Hz, 1H), 2.87 (t, J=7.5 Hz, 2H), 2.51 (s, 3H), 1.66-1.74 (m, 2H), 1.22-1.38 (m, 12H), 0.87 (t, J=7.0 Hz, 3H).

Aldehyde 74

3-Methyl-4-(4-(nonyl)benzoyl)benzaldehyde

The title compound was prepared using procedures analogous to those used to prepare Aldehyde 73 substituting 4-(nonyl)benzaldehyde for n-decanal in Step B: ^{1}H NMR (500 MHz) δ 10.0 (s, 1H), 7.76 (d, J=7.8 Hz, 1H), 7.74 (s, 1H), 7.66 (d, J=7.8 Hz, 1H), 2.88 (t, J=7.5 Hz, 2H), 2.51 (s, 3H), 1.66-1.74 (m, 2H), 1.22-1.38 (m, 10H), 0.88 (t, J=7.0 Hz, 3H).

Aldehyde 75

3'-(1-Hydroxyhept-1-yl)-4-biphenylcarboxaldehyde

Step A: 1-Bromo-3-(1-hydroxyhept-1-yl)benzene

Hexylmagnesium bromide (2.0M in THF, 3.7 mL, 7.4 mmol) was added to a solution of 3-bromobenzaldehyde (1.50g, 8.11 mmol) in tetrahydrofuran (10 mL) at –78 °C. After 10 min, the reaction was quenched by the addition of 2N

hydrochloric acid (30 mL) and the product extracted into ethyl acetate (30 mL). The organic layer was washed with sat'd sodium chloride (25 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 17% ethyl acetate/hexane gave 1.42 g (5.25 mmol, 65%) of product.

Step B: 3'-(1-Hydroxyhept-1-yl)-4-biphenylcarboxaldehyde

To a solution of 1-bromo-3-(1-hydroxyhept-1-yl)benzene (1.00 g, 3.70 mmol, from Step A), 4-formylphenylboronic acid (0.83 g, 5.55 mmol) and potassium fluoride (0.65 g, 11.10 mmol) in tetrahydrofuran (10 mL) was added palladium(II) acetate (0.016 g, 0.071 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.052 g, 0.148 mmol). After stirring for 24 h at rt, the reaction was diluted with ethyl acetate (50 mL), washed with water (50 mL), sat'd sodium chloride (50 mL), dried over magnesium sulfate and concentrated in vacuo. Silica gel chromatography eluting with 25% ethyl acetate/hexanes gave 0.81 g of product as a yellow oil.

Aldehyde 76

3'-(Heptanoyl)-4-biphenylcarboxaldehyde

Step A: 1-Bromo-3-heptanoyl benzene

Dess-Martin periodinane (4.40 g, 15% solution in methylene chloride, 1.56 mmol) was added to a solution of 1-bromo-3-(1-hydroxyhept-1-yl)benzene (0.39 g, 1.42 mmol, from Aldehyde 75, Step A). After 1 h, the reaction was quenched by the addition of 1N sodium hydroxide (20 mL). The aqueous layer was separated, washed with methylene chloride (20 mL) and the organic layers combined, dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with 5% ethyl acetate/hexane gave 0.30 g (1.11 mmol, 78%) of product: ^{1}H NMR (500 MHz) δ 8.08 (t, J=1.7 Hz, 1H), 7.87 (d, J=7.7 Hz, 1H), 7.68 (d, J=8.0 Hz, 1H), 7.34 (t, J=7.9 Hz, 1H), 2.93 (t, J=7.4 Hz, 2H), 1.68-1.76 (m, 2H), 1.28-1.40 (m, 6H), 0.89 (t, J=7.0 Hz, 3H).

Step B: 3'-(Heptanoyl)-4-biphenylcarboxaldehyde

To a solution of 1-bromo-3-heptanoyl benzene (0.30 g, 1.11 mmol, from Step A), 4-formylphenylboronic acid (0.25 g, 1.68 mmol) and potassium fluoride (0.20 g, 3.36 mmol) in tetrahydrofuran (2.5 mL) was added palladium(II) acetate (0.006 g, 0.025 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.016 g, 0.050 mmol). After stirring for 3 h at 50°C, the reaction was placed onto silica gel and

eluted with 10% ethyl acetate/hexanes to give 0.26 g (0.88 mmol, 80%) of product as a yellow oil: ^{1}H NMR (500 MHz) δ 8.22 (t, J=1.7 Hz, 1H), 7.90-8.10 (m, 3H), 8.30 (d, J=8.0 Hz, 1H), 7.99 (d, J=8.3 Hz, 2H), 7.58 (t, J=7.8 Hz, 1H), 3.02 (t, J=7.4 Hz, 2H), 1.66-1.80 (m, 2H), 1.38-1.44 (m, 2H), 1.30-1.38 (m, 4H), 0.90 (t, J=7.0 Hz, 3H).

Aldehyde 77

3-(Cyclopropyloxy)-4-(nonyloxy)benzaldehyde

To a solution of 1.78 g (10.0 mmol) of 3-(cyclopropyloxy)-4-hydroxybenzaldehyde and 2.54 g(10.0 mmol) of 1-iodononane in 20 mL acetonitrile was added 3.58 g(11.0 mmol) of Cs_2CO_3. The slurry was stirred at rt for 12 h. The reaction was quenched with 30 mL of water and extracted with ethyl acetate (50 mL x 2). The combined extractions were washed with water, dried with sodium sulfate and concentrated to a solid. Flash chromatography on a Biotage 40M cartridge using 10 % ethyl acetate/hexanes afforded 2.9 g (95%) of the title compound as a white solid. ^{1}H NMR (500 Mhz) δ 0.87-0.91 (m, 7H), 1.30-1.90 (m, 14H), 3.85 (m, 1H), 4.10 (t, J = 6.9, 2H), 6.98 (d, J = 8.2, 1H), 7.48 (dd, J = 8.5, 1.8, 1H), 7.77 (d, J = 1.8, 1H), 9.89 (s, 1H); LC-1: 4.6 min; ESI-MS 305 (M+H).

Aldehyde 78

4-(Nonylthio)benzaldehyde

To a solution of 3.15 g (10.0 mmol) of 1-bromo-4-(nonylthio)benzene in 50 mL anhydrous THF was slowly added 9.4 mL of *n*-BuLi (1.6 M in hexanes, 15 mmol) at –50 °C. The mixture was aged at the same temperature for 1 h before the addition of 2.3 mL of anhydrous DMF. The reaction mixture was allowed to warm to 0 °C and was quenched with 2 N HCl to pH=1. The layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic layer and extractions were washed with water and concentrated to oil. Flash chromatography on a Biotage 40M cartridge using 5 % ethyl acetate/hexanes afforded 2.35 g (89%) of the title compound as light yellow oil: ^{1}H NMR (500 MHz) δ 0.91 (t, J = 7.0, 3H), 1.30-1.76 (m, 14H), 3.03 (t, J = 7.4, 2H), 7.37 (d, J = 8.5, 2H), 7.78 (d, J = 8.5, 2H), 9.95 (s, 1H); LC-1: 4.8 min; ESI-MS 265 (M+H).

Aldehyde 79

3-(4-(Formyl)phenyl)-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

Step A: (E/Z)-2-Phenyl-3-chloro-4,4,4-trifluoro-2-butanal

Phosphorous oxychloride (7.5 mL, 80 mmol) was added to 15 mL of DMF at 0 °C. The resulting mixture was warmed to rt and stirred for 1 h. A solution of 5.0 g (26.6 mmol) of 1,1,1-trifluoromethyl-3-phenyl-2-propanone in 1 mL of DMF was added and the resulting mixture was stirred at 70 °C for 20 h. The reaction mixture was cooled to rt, poured onto 150 g of ice and stirred at ambient temperature for 1 h. The quenched mixture was extracted with 200 mL of ether. The extract was washed with 200 mL of water, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (4L) as the eluant afforded 5:1 g (82%) of the title compound.

Step B: Ethyl (4-phenyl-5-trifluoromethyl)thiophene-2-carboxylate

Ethyl mercaptoacetate (2.75 mL, 25.0 mmol) was added to a suspension of 600 mg (25 mmol) of NaH in 45 mL of THF maintaining the internal temperature at 25 °C. A solution of 5.10 g (21.7 mmol) of (E/Z)-2-phenyl-3-chloro-4,4,4-trifluoro-2-butanal (from Step A) was added and the resulting mixture was stirred at rt for 20 h. The reaction was quenched with 50 mL of sat'd NH_4Cl and the resulting mixture was partitioned between 250 mL of ether and 100 mL of water. The organic layer was separated, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (1L), then 4:1 v/v hexanes/CH_2Cl_2 (1L) as the eluant afforded 5.10 g (78%) of the title compound: ^{1}H NMR (400 Mhz) δ 1.40 (t, J= 7.2, 3H), 4.39 (q, J= 7.2, 2H), 7.42 (app s, 5H), 7.74 (q, J=1.6, 1H).

Step C: (4-Phenyl-5-trifluoromethyl)thiophene-2-carboxylic acid

A solution of 5.10 g (17.0 mmol) of ethyl 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylate (from Step B) in 20 mL of EtOH was treated with 10 mL of 5.0 N NaOH and stirred at rt for 30 min. The EtOH was removed in vacuo. The residual aqueous mixture was acidified to pH 2 with 1 N HCl, then extracted with 300 mL of 1:1 v/v EtOAc/ether. The extract was separated, dried and concentrated. Recrystallization from 200 mL of 20:1 v/v hexanes/ether afforded 4.30 g (93%) of the title compound: ^{1}H NMR (500 Mhz) δ 7.43 (app s, 5H), 7.84 (app s, 1H); ^{13}C NMR ($CDCl_3$, 125 Mhz) δ 121.7 (q, J= 269), 128.5, 128.6, 128.8, 132.5 (q, J= 36), 133.3, 133.8, 137.5, 144.8, 167.0.

Step D: 3-[4-(Carbomethoxy)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A solution of 408 mg (1.5 mmol) of 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylic acid and 1 mL of oxalyl chloride in 5 mL of CH_2Cl_2 was treated with 5 drops of DMF. The resulting mixture was stirred at rt for 1 h, then concentrated. The crude acid chloride and 291 mg (1.5 mmol) of 4-(carbomethoxy)benzamidoxime were dissolved in 7 mL of 6:1 v/v xylenes/pyridine. The resulting solution was heated at 140 °C for 1 h, then cooled. The mixture was partitioned between 50 mL of 1:1 EtOAc/ether and 50 mL of 1 N HCl. The organic layer was separated, washed with 3 x 50 mL of 1 N HCl, 50 mL of sat'd $NaHCO_3$, dried and concentrated. Chromatography on a Biotage 40 M cartridge using hexanes (1L), then 20:1 v/v hexanes/EtOAc (1L) as the eluant afforded 423 mg (65%) of the title compound: ^{1}H NMR (500 Mhz) δ 3.97 (s, 3H), 7.48 (app s, 5H), 7.92 (s, 1H), 8.18 (app d, J= 8.5, 2H), 8.23 (app d, J= 8.5, 2H).

Step E: 3-[4-(Hydroxymethyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A solution of 390 mg (0.91 mmol) of 3-[4-(carbomethoxy)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole (from Step D) in 10 mL of CH_2Cl_2 at –78 °C was treated with 2.7 mL of 1.0 M DIBALH solution in CH_2Cl_2. The resulting solution was stirred cold for 1 h, then quenched with 5 mL of sat'd Rochelle salt solution. The mixture was partitioned between 100 mL CH_2Cl_2 and 50 mL of 1 N NaOH. The organic layer was separated, dried and concentrated. Chromatography on a Biotage 40 S cartridge using 4:1 v/v hexanes/EtOAc (1L) as the eluant afforded 325 mg (89%) of the title compound: ^{1}H NMR (500 Mhz) δ 1.80 (app s, 1H), 4.80 (d, J= 4.0, 2H), 7.46-7.48 (5H), 7.52 (d, J= 8.0, 2H), 7.91 (q, J= 1.5, 1H), 8.14 (d, J= 8.0, 2H).

Step F: 3-[4-(Formyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole

A mixture of 310 mg (0.77 mmol) of 3-[4-(hydroxymethyl)phenyl]-5-(4-phenyl-5-trifluoromethyl-2-thienyl)-1,2,4-oxadiazole (from Step E), 527 mg (1.5 mmol) of 4-methylmorpholine N-oxide and 500 mg of 4 A molecular sieves in 15 mL of CH_3CN was treated with 12 mg (0.034 mmol) of tetrapropylammonium perruthnate and the resulting mixture was stirred ar rt for 2 h. The solids were filtered and the

filtrated was concentrated. Chromatography on a Biotage 40 S cartridge using 9:1 v/v hexanes/EtOAc (1L) as the eluant afforded 205 mg (66%) of the title compound: ^{1}H NMR (500 Mhz) δ 7.48 (app s, 5H), 7.93 (app s, 1H), 8.03 (d, J= 8.5, 2H), 8.33 (d, J= 8.5, 2H), 10.1 (s, 1H).

Aldehyde 80

4-[(4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy]benzaldehyde

Step A: 2-Hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene

A solution of 2.10 g (7.7 mmol) of 4-phenyl-5-trifluoromethyl-thiophene-2-carboxylic acid (from Aldehyde 17, Step C) in 20 mL of THF was treated with 5.0 mL of 2.0 M borane dimethylsulfide complex in THF. The resulting solution was heated at reflux for 3 h, cooled to rt, quenched with 10 mL of MeOH and concentrated. Chromatography on a Biotage 40M cartridge using 9:1 v/v hexanes/EtOAc as the eluant afforded 1.95 g (98%) of the title compound: ^{1}H NMR (500 Mhz) δ 2.05 (app s, 1H), 4.87 (s, 2H), 6.99 (s, 1H), 7.41 (app s, 5H).

Step B: 4-((4-Phenyl-5-trifluoromethyl-2-thienyl)methoxy)benzaldehyde

A solution of 1.95 g (7.5 mmol) of 2-hydroxymethyl-4-phenyl-5-trifluoromethyl-thiophene (from Step A), 925 mg (7.6 mmol) of 4-hydroxybenzaldehyde and 3.0 g (11.4 mmol) of triphenylphosphene in 40 mL of THF at 0 °C was treated with 2.0 g (11.4 mmol) of diethylazodicarboxylate. The resulting mixture was warmed to rt, stirred for 2 h, then concentrated. Chromatography on a Biotage 75S cartridge using 9:1 v/v heptane/EtOAc as the eluant afforded 2.5 g of impure title compound. Chromatography on a Biotage 40M cartridge using 19:1 v/v hexanes/EtOAc (1L), then 4:1 v/v hexanes/EtOAc (1L) as the eluant afforded 1.65 g (60%) of the title compound: ^{1}H NMR (500 Mhz) δ 5.32 (s, 2H), 7.10 (d, J= 8.5, 2H), 7.12 (s, 1H), 7.41-7.43 (5H), 7.85-7.90 (2H), 9.92 (s, 1H).

PREPARATION OF EXAMPLES

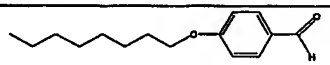
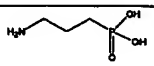
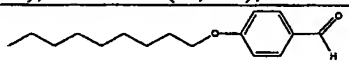
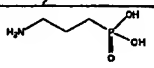
EXAMPLE 1

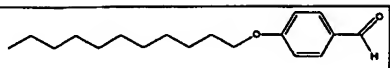
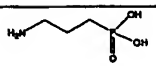
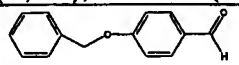
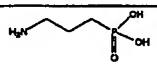
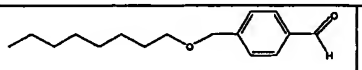
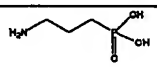
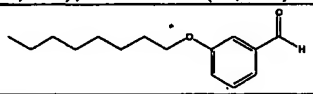
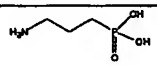
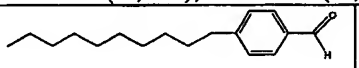
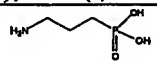
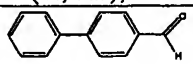
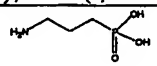
N-((4-Decyloxy)benzyl)-3-aminopropylphosphonic acid

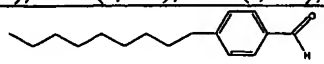
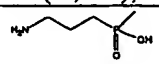
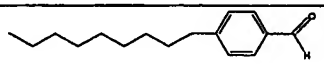
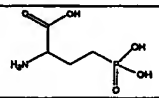
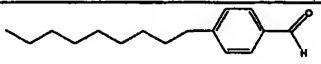
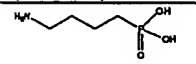
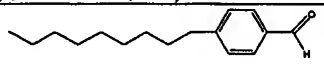
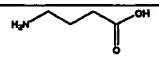
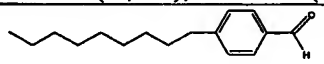
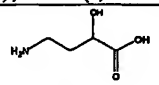
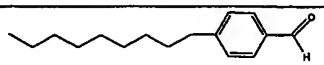
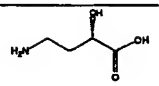
3-Aminopropylphosphonic acid (0.064 g, 0.457 mmol) and tetrabutylammonium hydroxide (1.0M in methanol, 0.46 mL, 0.46 mmol) in methanol (3 mL) were heated at 50 °C for 1 h to dissolve all solids. 4-(Decyloxy)benzaldehyde (0.100g, 0.381 mmol) and sodium cyanoborohydride (0.025 g, 0.40 mmol) were added and stirring was continued for 1 h at 50 °C. The reaction mixture was made acidic (pH~5) by the addition of concentrated HCl then directly purified by LC-3 to give the title compound (0.055 g): ^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.7 Hz, 2H), 6.98 (d, J=8.7 Hz, 2H), 4.12 (s, 2H), 3.99 (t, J=6.4 Hz, 2H), 3.12 (t, J=7.7 Hz, 2H), 2.0 (m, 2H), 1.64-1.84 (m, 4H), 1.47 (m, 2H), 1.24-1.40 (m, 12H), 0.90 (t, J=6.9 Hz, 3H); MS *m/e* 386.4 (M+H).

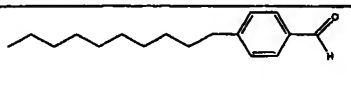
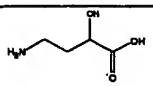
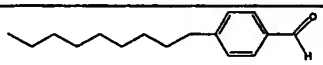
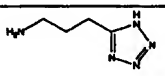
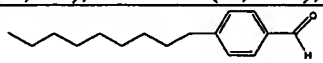
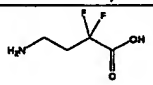
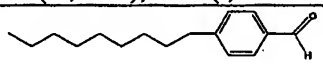
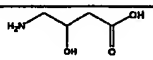
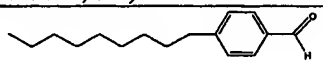
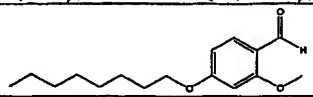
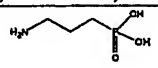
EXAMPLES 2-107

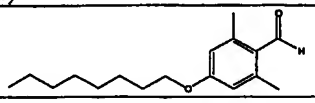
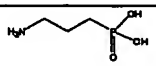
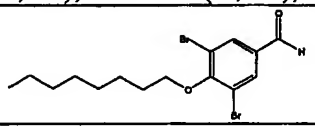
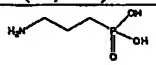
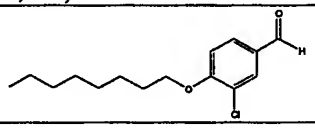
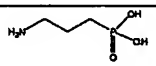
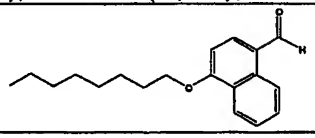
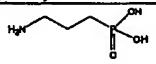
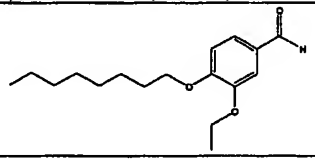
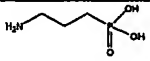
The following Examples (2-112) were prepared using a procedure analogous to that described in EXAMPLE 1 substituting A for 4-(decyloxy)benzaldehyde and B for 3-aminopropylphosphonic acid.

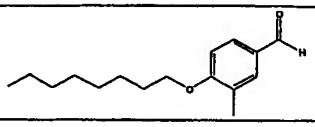
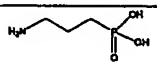
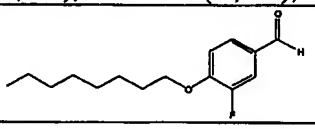
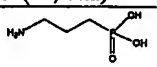
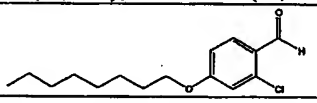
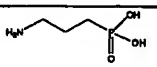
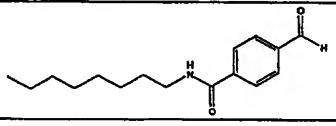
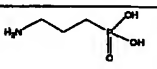
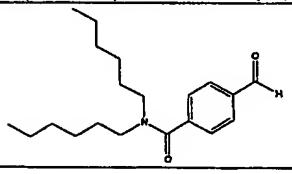
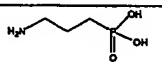
EXAMPLE	A	B	ESI-MS
2			358.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.35-7.41 (m, 2H), 6.94-7.01 (m, 2H), 4.08-4.13 (m, 2H), 3.96-4.02 (m, 2H), 3.08-3.14 (m, 2H), 1.93-2.04 (m, 2H), 1.73-1.82 (m, 4H), 1.43-1.51 (m, 2H), 1.26-1.41 (m, 8H), 0.87-0.94 (m, 3H).			
3			372.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, 2H), 6.98 (d, 2H), 4.86 (s, 19H), 4.12 (s, 2H), 3.98 (t, 2H), 3.12 (t, 2H), 1.94-2.04 (m, 2H), 1.72-1.84 (m, 4H), 1.42-1.52 (m, 2H), 1.24-1.41 (m, 8H), 0.90 (t, 3H).			

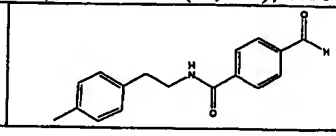
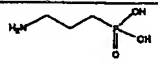
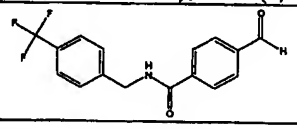
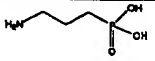
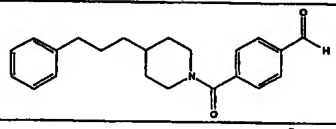
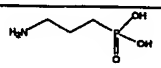
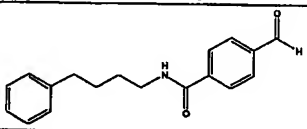
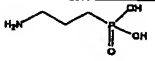
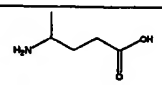
4			400.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.36-7.40 (m, 2H), 6.95-7.01 (m, 2H), 4.12 (s, 2H), 3.95-4.02 (m, 2H), 3.09-3.15 (m, 2H), 1.94-2.04 (m, 2H), 1.72-1.84 (m, 4H), 1.42-1.52 (m, 2H), 1.24-1.42 (m, 8H), 0.87-0.94 (m, 3H).			
5			336.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.33-7.44 (m, 5H), 7.27-7.33 (m, 2H), 7.03-7.09 (m, 2H), 5.11 (s, 2H), 4.11 (s, 2H), 3.07-3.15 (m, 2H), 1.92-2.04 (m, 2H), 1.73-1.82 (m, 2H).			
6			372.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.42-7.50 (m, 4H), 4.52 (s, 2H), 4.18 (s, 2H), 3.46-3.52 (m, 2H), 3.11-3.18 (m, 2H), 1.95-2.06 (m, 2H), 1.75-1.85 (m, 2H), 1.56-1.64 (m, 2H), 1.25-1.34 (m, 6H), 0.85-0.92 (m, 3H).			
7			358.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.34 (t, J=7.9 Hz, 1H), 7.05 (d, J=2.3 Hz, 1H), 7.03 (d, J=7.8 Hz, 1H), 6.98 (dd, J=2.3, 8.4 Hz), 4.12 (s, 2H), 4.00 (t, J=6.5 Hz, 2H), 3.12 (t, J=6.9 Hz, 2H), 1.94-2.20 (m, 2H), 1.70-1.82 (m, 4H), 1.44-1.52 (m, 2H), 1.26-1.40 (m, 8H), 0.90 (t, J=6.9 Hz, 3H).			
8			342.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.14 (t, J=7.7 Hz, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.00 (m, 2H), 1.81 (td, J= 7.6, 18.5 Hz, 2H), 1.58-1.64 (m, 2H), 1.22-1.36 (m, 10H), 0.89 (t, J=7.0 Hz, 3H).			
9			370.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.14 (t, J=7.7 Hz, 2H), 2.64 (t, J= 7.6 Hz, 2H), 2.00 (m, 2H), 1.80 (td, J= 7.6, 18.5 Hz, 2H), 1.56-1.64 (m, 2H), 1.24-1.38 (m, 14H), 0.89 (t, J=7.0 Hz, 3H).			
11			306.1

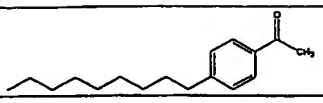
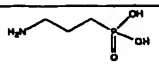
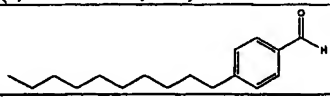
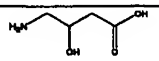
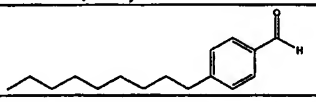
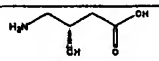
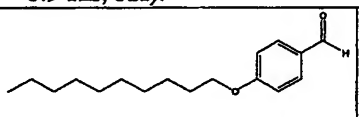
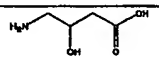
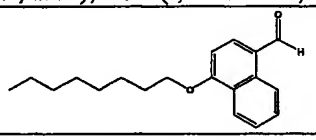
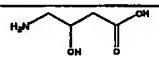
^{1}H NMR (500 MHz , CD_3OD) δ 7.72 (m, 2H), 7.63 (m, 2H), 7.56 (m, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 4.24 (s, 2H), 3.18 (t, 2H), 1.97-2.08 (m, 2H), 1.76-1.86 (m, 2H).			
12			354.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.3 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.12 (t, J=7.3 Hz, 2H), 2.64 (t, J= 7.6 Hz, 2H), 1.98 (m, 2H), 1.76-1.84 (m, 2H), 1.58-1.64 (m, 2H), 1.43 (d, J=14 Hz, 3H), 1.24-1.36 (m, 12H), 0.89 (t, J=7.0 Hz, 3H).			
13			400.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.41 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.14-4.22 (m, 2H), 4.04 (t, J=6.0 Hz, 1H), 2.64 (t, J= 7.6 Hz, 2H), 2.20-2.30 (m, 2H), 1.74-1.98 (m, 2H), 1.58-1.64 (m, 2H), 1.24-1.32 (m, 12H), 0.90 (t, J=7.0 Hz, 3H).			
14			370.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.1 Hz, 2H), 4.15 (s, 2H), 3.05 (t, J=7.8 Hz, 2H), 2.64 (t, J= 7.7 Hz, 2H), 1.58-1.984 (m, 8H), 1.24-1.36 (m, 12H), 0.89 (t, J=7.0 Hz, 3H).			
15			320.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.10 (t, J=7.8 Hz, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.45 (t, J= 7.0 Hz, 2H), 1.93-1.99 (m, 2H), 1.56-1.64 (m, 2H), 1.24-1.34 (m, 12H), 0.89 (t, J=7.0 Hz, 3H).			
16			336.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.1 Hz, 2H), 7.28 (d, J=8.3 Hz, 2H), 4.26 (dd, J=4.1, 7.8 Hz, 1H), 4.17 (s, 2H), 3.16-3.22 (m, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.16-2.24 (m, 1H), 1.98-2.06 (m, 1H), 1.58-1.64 (m, 2H), 1.24-1.32 (m, 12H), 0.89 (t, J=7.0 Hz, 3H).			
17			336.2

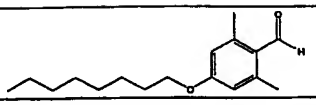
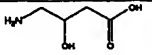
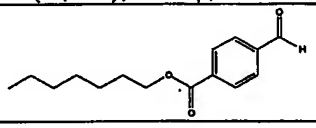
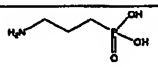
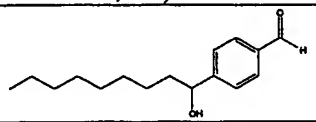
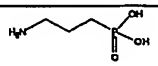
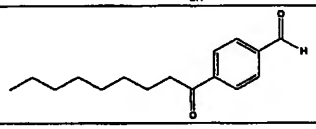
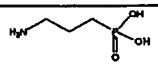
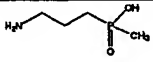
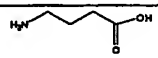
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.26 (dd, J=4.1, 8.0 Hz, 1H), 4.17 (s, 2H), 3.16-3.22 (m, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.16-2.24 (m, 1H), 1.98-2.06 (m, 1H), 1.58-1.64 (m, 2H), 1.24-1.32 (m, 12H), 0.89 (t, J=7.0 Hz, 3H)			
18			350.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.26 (dd, J=4.3, 8.0 Hz, 1H), 4.17 (s, 2H), 3.16-3.22 (m, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.16-2.24 (m, 1H), 1.98-2.06 (m, 1H), 1.58-1.64 (m, 2H), 1.24-1.32 (m, 14H), 0.89 (t, J=7.0 Hz, 3H)			
19			344.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.38 (d, J=7.0 Hz, 2H), 7.28 (d, J=7.8 Hz, 2H), 4.18 (s, 2H), 3.17 (t, J=7.4 Hz, 2H), 3.06 (t, J=7.4 Hz, 2H), 2.64 (t, J= 7.6 Hz, 2H), 2.20 (m, 2H), 1.56-1.64 (m, 2H), 1.22-1.36 (m, 12H), 0.89 (t, J=7.0 Hz, 3H)			
20			356.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.2 Hz, 2H), 7.03 (d, J=7.8 Hz, 1H), 4.20 (s, 2H), 2.65 (t, J=7.7 Hz, 2H), 2.49-2.60 (m, 2H), 1.58-1.64 (m, 2H), 1.24-1.34 (m, 14H), 0.89 (t, J=7.0 Hz, 3H)			
21			336.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.3 Hz, 2H), 4.25-4.31 (m, 1H), 4.19 (s, 2H), 3.18 dd, J=2.9, 12.5 Hz, 1H), 2.98 (dd, J= 9.9, 12.6 Hz, 1H), 2.64 (t, J=7.7 Hz, 2H), 2.53 (d, J=6.2 Hz, 2H), 1.56-1.64 (m, 2H), 1.24-1.34 (m, 12H), 0.89 (t, J=7.0 Hz, 3H)			
22			338.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.40 (d, J=8.0 Hz, 2H), 7.30 (d, J=7.7 Hz, 2H), 5.14-5.32 (m, 1H), 4.23 (m, 2H), 3.34-3.42 (m, 2H), 2.74-2.82 (m, 2H), 2.65 (t, J= 7.7Hz, 2H), 1.56-1.63 (m, 2H), 1.24-1.36 (m, 12H), 0.89 (t, J=7.0 Hz, 3H)			
23			388.1

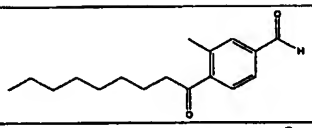
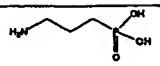
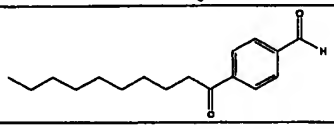
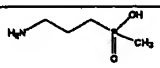
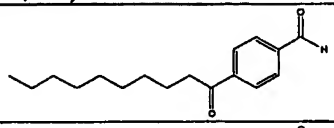
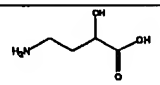
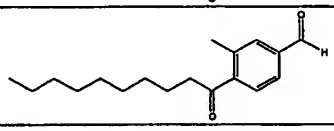
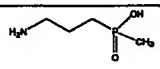
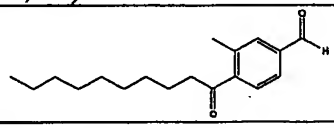
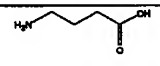
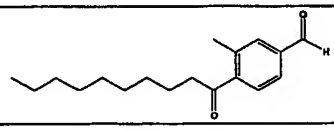
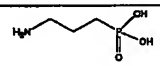
^{1}H NMR (500 MHz , CD_3OD) δ 7.24-7.28 (m, 1H), 6.60-6.63 (m, 1H), 6.53-6.57 (m, 1H), 4.11 (s, 2H), 3.96-4.02 (m, 2H), 3.88-3.92 (m, 3H), 3.28-3.33 (m, 2H), 3.06-3.12 (m, 2H), 1.94-2.05 (m, 2H), 1.72-1.82 (m, 4H), 1.43-1.52 (m, 2H), 1.26-1.41 (m, 8H), 0.87-0.94 (m, 3H)			
24			386.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.68 (s, 2H), 4.20-4.25 (m, 2H), 3.91-3.97 (m, 2H), 3.22-3.27 (m, 2H), 2.41 (s, 6H), 1.99-2.10 (m, 2H), 1.78-1.87 (m, 2H), 1.69-1.78 (m, 2H), 1.41-1.50 (m, 2H), 1.26-1.40 (m, 8H), 0.86-0.94 (m, 3H)			
25			516.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.78 (s, 2H), 4.14 (s, 2H), 4.00-4.05 (m, 2H), 3.12-3.18 (m, 2H), 1.94-2.04 (m, 2H), 1.76-1.90 (m, 4H), 1.52-1.59 (m, 2H), 1.29-1.44 (m, 8H), 0.88-0.94 (m, 3H)			
26			392.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.52-7.54 (m, 1H), 7.34-7.38 (m, 1H), 7.08-7.13 (m, 1H), 4.04-4.14 (m, 4H), 3.09-3.16 (m, 2H), 1.93-2.04 (m, 2H), 1.73-1.85 (m, 4H), 1.46-1.55 (m, 2H), 1.26-1.42 (m, 8H), 0.87-0.94 (m, 3H)			
27			408.3
^{1}H NMR (500 MHz , CD_3OD) δ 8.35-8.38 (m, 1H), 8.05-8.09 (m, 1H), 7.64-7.70 (m, 1H), 7.54-7.62 (m, 2H), 6.94-6.98 (m, 1H), 4.61 (s, 2H), 4.18-4.24 (m, 2H), 3.21-3.27 (m, 2H), 1.99-2.08 (m, 2H), 1.91-1.99 (m, 2H), 1.75-1.85 (m, 2H), 1.55-1.64 (m, 2H), 1.27-1.48 (m, 8H), 0.87-0.94 (m, 3H)			
28			402.2

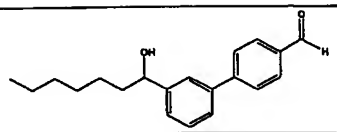
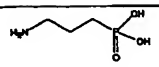
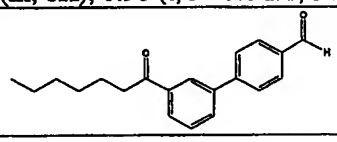
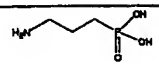
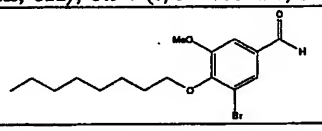
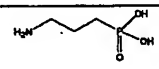
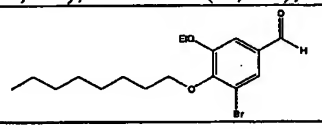
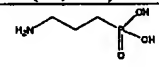
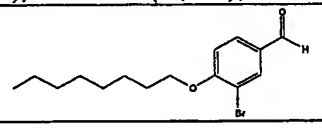
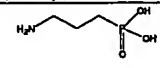
^{1}H NMR (500 MHz , CD_3OD) δ 7.05-7.08 (m, 1H), 6.98-7.01 (m, 2H), 4.06-4.14 (m, 3H), 3.98-4.04 (m, 2H), 3.28-3.32 (m, 2H), 3.08-3.15 (m, 2H), 1.94-2.04 (m, 2H), 1.72-1.84 (m, 4H), 1.45-1.52 (m, 2H), 1.38-1.44 (m, 2H), 1.26-1.38 (m, 8H), 0.86-0.94 (m, 3H)			
29			372.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.22-7.27 (m, 2H), 6.91-6.95 (m, 1H), 4.07 (s, 2H), 3.97-4.03 (m, 2H), 3.07-3.14 (m, 2H), 2.22 (s, 3H), 1.93-2.04 (m, 2H), 1.73-1.84 (m, 4H), 1.46-1.54 (m, 2H), 1.26-1.42 (m, 8H), 0.86-0.93 (m, 3H)			
30			
^{1}H NMR (500 MHz , CD_3OD) δ 7.19-7.28 (m, 2H), 7.11-7.16 (m, 1H), 4.11 (s, 2H), 4.03-4.08 (m, 2H), 3.09-3.15 (m, 2H), 1.93-2.04 (m, 2H), 1.72-1.84 (m, 4H), 1.44-1.54 (m, 2H), 1.26-1.42 (m, 8H), 0.86-0.94 (m, 3H)			
31			392.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.48 (d, J=8.5 Hz, 1H), 7.09 (d, J=2.3 Hz, 1H), 6.96 (dd, J=2.6, 8.6, 1H), 4.28 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.29-3.30 (m, 2H), 3.18 (t, J=7.4 Hz, 2H0, 1.97-2.08 (m, 2H), 1.73-1.84 (m, 4H0, 1.42-1.52 (m, 2H), 1.26-1.41 (m, 8H), 0.87-0.94 (m, 3H)			
32			385.4
^{1}H NMR (500 MHz , CD_3OD) δ 7.86-7.91 (m, 2H), 7.56-7.60 (m, 2H), 4.24 (s, 2H), 3.34-3.40 (m, 2H), 3.14-3.19 (m, 2H), 1.95-2.07 (m, 2H), 1.74-1.84 (m, 2H), 1.58-1.67 (m, 2H), 1.25-1.43 (m, 10H), 0.86-0.92 (m, 3H)			
33			441.5

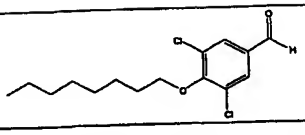
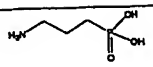
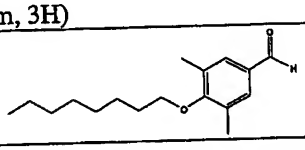
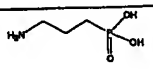
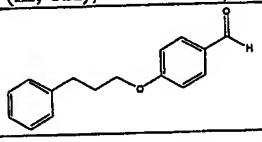
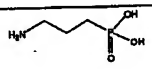
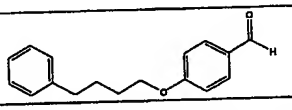
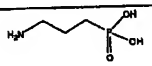
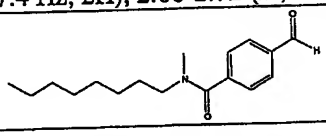
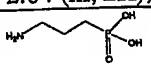
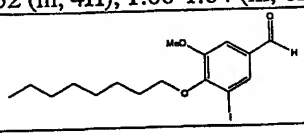
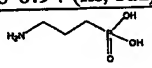
^{1}H NMR (500 MHz , CD_3OD) δ 7.56-7.60 (m, 2H), 7.42-7.46 (m, 2H), 4.23 (s, 2H), 3.46-3.52 (m, 2H), 3.20-3.26 (m, 2H), 3.14-3.20 (m, 2H), 1.94-2.06 (m, 2H), 1.73-1.84 (m, 2H), 1.64-1.72 (m, 2H), 1.45-1.56 (m, 2H), 1.32-1.44 (m, 8H), 1.18-1.27 (m, 2H), 1.04-1.18 (m, 2H), 0.88-0.98 (m, 3H), 0.80-0.88 (m, 3H)			
34			391.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.85 (d, J=8.3 Hz, 2H), 7.57 (d, J=8.2 Hz, 2H), 7.12 (d, J=8.1Hz, 2H), 7.09 (d, J=8.0 Hz, 2H), 4.25 (s, 2H), 3.58 (t, J=7.4 Hz, 2H), 3.17 (t, J=7.6 Hz, 2H), 2.87 (t, J=7.5, 2H), 2.28 (s, 3H), 1.98-2.03 (m, 2H), 1.79-1.84 (m, 2H)			
35			431.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.95 (d, J=8.3 Hz, 2H), 7.63 (d, J=8.0, 2H), 7.60 (d, J=8.2, 2H), 7.54 (d, J=8.0 Hz, 2H), 4.65 (s, 2H), 4.26 (s, 2H). 3.17 (t, J=7.3, 2H), 1.98-2.06 (m, 2H), 1.75-1.84 (m, 2H)			
36			459.2
37			405.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.88 (d, J=8.2 Hz, 2H), 7.57 (d, J=8.2 Hz, 2H), 7.23 (t, J=7.5, 2H), 7.18 (d, J=7.1, 2H), 7.13 (t, J=7.2 Hz, 1H), 4.24 (s, 2H), 3.37-3.43 (m, 2H), 3.13-3.20 (m, 2H), 2.62-2.70 (m, 2H), 1.95-2.06 (m, 2H), 1.74-1.84 (m, 2H), 1.60-1.74 (m, 4H)			
38			334.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.2 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.21 (d, J=13.0 Hz, 1H), 4.18 (d, J=13.0 Hz, 1H), 3.32-3.40 (m, 1H), 2.64 (t, J=7.7 Hz, 2H), 2.52 (ddd, J=16.9, 7.5, 6.2 Hz, 1H), 2.43 (dt, J=17.2, 7.7 Hz, 1H), 2.12-2.20 (m, 1H), 1.76-1.86 (m, 1H), 1.56-1.65 (m, 2H), 1.38 (d, J=6.7 Hz, 3H), 1.22-1.34 (m, 12H), 0.90 (t, J= 6.3 Hz, 3H).			

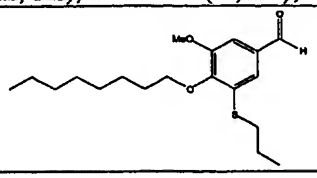
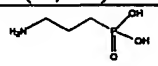
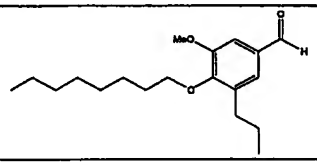
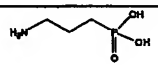
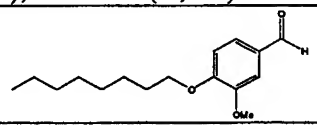
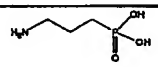
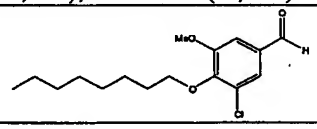
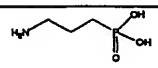
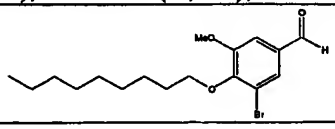
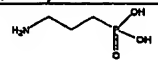
39			370.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.37 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 4.33 (q, J=6.8 Hz, 1H), 3.00-3.08 (m, 1H), 2.82-2.88 (m, 1H), 2.64 (t, J=7.7 Hz, 2H), 1.90-2.00 (m, 2H), 1.70-1.80 (m, 2H), 1.65 (d, J= 6.9 Hz, 3H), 1.58-1.64 (m, 2H), 1.22-1.36 (m, 12H), 0.89 (t, J= 6.9 Hz, 3H).			
40			350.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.24-4.30 (m, 1H), 4.19 (s, 2H), 3.17 (dd, J=12.6, 3.0 Hz, 1H), 2.98 (dd, J=12.9, 9.9 Hz, 1H), 2.64 (t, J=7.7 Hz, 2H), 2.52 (d, J=6.1 Hz, 2H), 1.58-1.65 (m, 2H), 1.24-1.35 (m, 14H), 0.89 (t, J= 7.0 Hz, 3H).			
41			336.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.24-4.30 (m, 1H), 4.19 (s, 2H), 3.17 (dd, J=12.6, 3.1 Hz, 1H), 2.98 (dd, J=12.9, 9.8 Hz, 1H), 2.64 (t, J=7.7 Hz, 2H), 2.52 (d, J=6.1 Hz, 2H), 1.58-1.65 (m, 2H), 1.24-1.35 (m, 12H), 0.89 (t, J= 6.9 Hz, 3H).			
42			366.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.7 Hz, 2H), 6.98 (d, J=8.7 Hz, 2H), 4.25-4.30 (m, 1H), 4.16 (s, 2H), 3.99 (t, J=6.5 Hz, 2H), 3.16 (dd, J=12.5, 2.9 Hz, 1H), 2.96 (dd, J=12.8, 9.8 Hz, 1H), 2.52 (d, J=6.2 Hz, 2H), 1.74-1.80 (m, 2H), 1.44-1.51 (m, 2H), 1.22-1.40 (m, 12H), 0.90 (t, J= 7.0 Hz, 3H).			
43			388.1
^{1}H NMR (500 MHz , CD_3OD) δ 8.35 (d, J=8.5 Hz, 1H), 8.09 (d, J=8.5 Hz, 1H), 7.67 (t, J=8.4 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.57 (t, J=8.0 Hz, 1H), 6.96 (d, J=8.0 Hz, 1H), 4.66 (s, 2H), 4.32-4.38 (m, 1H) 4.21 (t, J=6.4 Hz, 2H), 3.26-3.32 (m, 1H), 3.08 (dd, J=12.8, 9.8 Hz, 1H), 2.55 (d, J=6.2 Hz, 2H), 1.91-1.98 (m, 2H), 1.56-1.62 (m, 2H), 1.28-1.48 (m, 8H), 0.90 (t, J= 6.9 Hz, 3H).			

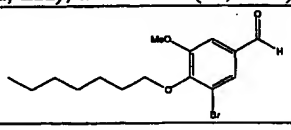
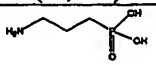
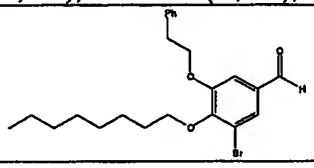
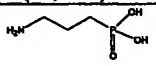
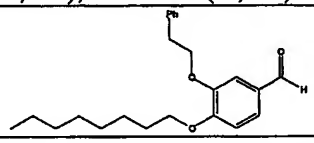
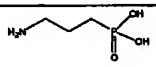
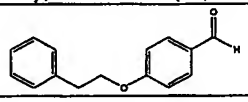
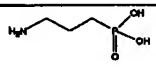
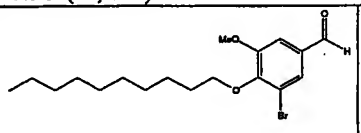
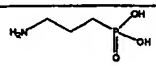
44			366.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.69 (s, 2H), 4.35-4.40 (m, 1H), 4.33 (d, J=13.8 Hz, 1H), 4.26 (d, J=13.7 Hz, 1H), 3.95 (t, J=6.5 Hz, 2H), 3.30-3.35 (m, 1H), 3.09 (dd, J=12.8, 9.9 Hz, 1H), 2.56 (d, J=6.2 Hz, 2H), 2.42 (s, 6H), 1.71-1.78 (m, 2H), 1.42-1.48 (m, 2H), 1.28-1.38 (m, 8H), 0.90 (t, J= 7.0 Hz, 3H).			
45			372.2
^{1}H NMR (500 MHz , CD_3OD) δ 8.12 (d, J=8.3 Hz, 2H), 7.65 (d, J=8.2 Hz, 2H), 4.36 (t, J=6.6 Hz, 2H), 4.30 (s, 2H), 3.21 (t, J=7.5 Hz, 2H), 2.00-2.10 (m, 4H), 1.32-1.52 (m, 8H), 0.93 (t, J= 7.0 Hz, 3H).			
46			372.2
47			370.2
^{1}H NMR (500 MHz , CD_3OD) δ 8.06 (d, J=8.3 Hz, 2H), 7.65 (d, J=8.3 Hz, 2H), 4.23 (s, 2H), 3.16 (t, J=6.1 Hz, 2H), 3.04 (t, J=7.4 Hz, 2H), 1.96-2.06 (m, 2H), 1.66-1.78 (m, 4H), 1.26-1.44 (m, 10H), 0.91 (t, J= 7.1 Hz, 3H).			
48			368.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.41 (d, J=8.0 Hz, 2H), 7.30 (d, J=8.0 Hz, 2H), 4.18 (s, 2H), 3.16 (t, J=7.4 Hz, 2H), 2.67 (t, J=7.7 Hz, 2H), 1.96-2.06 (m, 2H), 1.82-1.88 (m, 2H), 1.60-1.68 (m, 2H), 1.59 (d, J=14.2 Hz, 3H), 1.26-1.36 (m, 14H), 0.92 (t, J= 7.0 Hz, 3H).			
49			334.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.40 (d, J=8.1 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 4.18 (s, 2H), 3.12 (t, J=7.2 Hz, 2H), 2.67 (t, J=7.7 Hz, 2H), 2.48 (t, J=7.0 Hz, 2H), 1.94-2.02 (m, 2H), 1.60-1.68 (m, 2H), 1.26-1.38 (m, 14H), 0.92 (t, J= 7.0 Hz, 3H).			

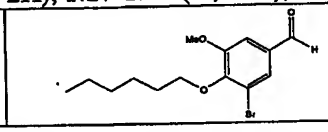
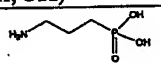
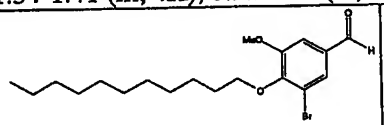
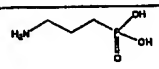
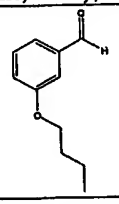
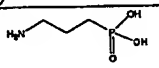
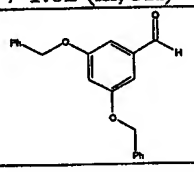
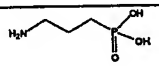
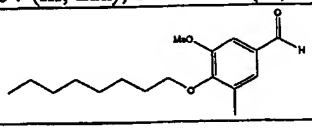
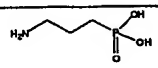
50			384.2
51			382.2
^{1}H NMR (500 MHz , CD_3OD) δ 8.30 (d, J=8.3 Hz, 2H), 7.65 (d, J=8.2 Hz, 2H), 4.25 (s, 2H), 4.30 (s, 2H), 3.20 (t, J=7.3 Hz, 2H), 3.01 (t, J=7.2 Hz, 2H), 2.00-2.08 (m, 2H), 1.82-1.90 (m, 2H), 1.68-1.76 (m, 2H), 1.48 (d, J=14.2 Hz, 3H), 1.26-1.44 (m, 12H), 0.92 (t, J= 7.1 Hz, 3H).			
52			364.1
53			396.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.77 (d, J=7.8 Hz, 1H), 7.42-7.43 (m, 2H), 4.22 (s, 2H), 3.17 (t, J=7.3 Hz, 2H), 2.93 (t, J=7.3 Hz, 2H), 2.48 (s, 3H), 1.96-2.06 (m, 2H), 1.82-1.88 (m, 2H), 1.64-1.70 (m, 2H), 1.47 (d, J=14.0 Hz, 3H), 1.28-1.38 (m, 12H), 0.90 (t, J= 7.0 Hz, 3H).			
54			362.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.76 (d, J=8.4 Hz, 1H), 7.41-7.43 (m, 2H), 4.23 (s, 2H), 3.14 (t, J=7.8 Hz, 2H), 2.93 (t, J=7.3 Hz, 2H), 2.48 (t, J=7.0 Hz, 2H), 2.47 (s, 3H), 1.96-2.04 (m, 2H), 1.64-1.70 (m, 2H), 1.26-1.40 (m, 12H), 0.91 (t, J= 7.0 Hz, 3H).			
55			398.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.76 (d, J=7.8 Hz, 1H), 7.42-7.43 (m, 2H), 4.21 (s, 2H), 3.18 (t, J=7.2 Hz, 2H), 2.93 (t, J=7.3 Hz, 2H), 2.48 (s, 3H), 1.98-2.08 (m, 2H), 1.80 (dt, J=18.1, 7.4 Hz, 2H), 1.64-1.71 (m, 2H), 1.26-1.40 (m, 12H), 0.91 (t, J= 7.0 Hz, 3H).			

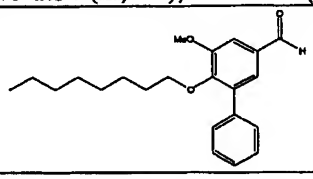
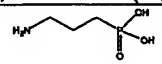
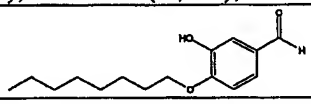
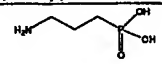
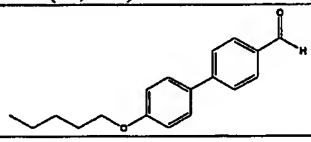
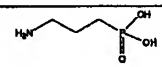
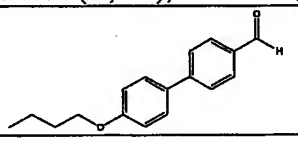
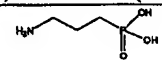
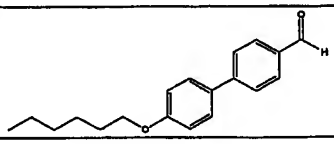
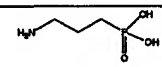
56			420.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.76 (d, J=8.3 Hz, 2H), 7.64 (s, 1H), 7.59 (d, J=8.3 Hz, 2H), 7.55 (d, J=7.7 Hz, 1H), 7.45 (t, J=7.7 Hz, 1H), 7.37 (d, J=7.6 Hz, 1H), 4.70 (t, 6.8 Hz, 1H), 4.27 (s, 2H), 3.21 (t, J=7.6 Hz, 2H), 2.00-2.10 (m, 2H), 1.70-1.88 (m, 4H), 1.26-1.50 (m, 8H), 0.90 (t, J= 7.0 Hz, 3H).			
57			418.3
^{1}H NMR (500 MHz , CD_3OD) δ 8.23 (s, 1H), 8.04 (d, J=7.7 Hz, 1H), 7.91 (d, J=7.8 Hz, 1H), 7.80 (d, J=8.2 Hz, 2H), 7.62-7.66 (m, 3H), 4.28 (s, 2H), 3.22 (t, 7.5 Hz, 2H), 3.11 (t, J=7.2 Hz, 2H), 2.02-2.12 (m, 2H), 1.84 (dt, J=18.3, 7.4 Hz, 2H), 1.72-1.78 (m, 2H), 1.28-1.48 (m, 6H), 0.94 (t, J= 7.0 Hz, 3H).			
58			468.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.29 (s, 1H), 7.16 (s, 1H), 4.01 (s, 2H), 3.98 (t, J=6.4 Hz, 2H), 3.90 (s, 3H), 3.13 (t, J=6.7 Hz, 2H), 1.98-2.01 (m, 2H), 1.73-1.77 (m, 4H), 1.49-1.51 (m, 2H), 1.32-1.34 (m, 8H), 0.89-0.91 (m, 3H)			
59			357.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.28 (s, 1H), 7.13 (s, 1H), 4.12-4.13 (m, 2H), 4.09 (s, 3H), 4.00 (t, J=6.3, 2H), 3.12 (t, J=6.7, 2H), 1.96-2.04 (m, 2H), 1.73-1.78 (m, 4H), 1.48-1.56 (m, 2H), 1.43-1.46 (m, 2H), 1.32-1.37 (m, 8H), 0.88-0.93 (m, 3H)			
60			436.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.7 (s, 1H), 7.41 (d, J=8.5 Hz, 1H), 7.07 (d, J=8.4 Hz, 1H), 4.06-4.10 (m, 4H), 3.12 (t, J=7.2, 2H), 1.95-2.00 (m, 2H), 1.75-1.83 (m, 4H), 1.51-1.54 (m, 2H), 1.32-1.37 (m, 8H), 0.89-0.91 (m, 3H)			

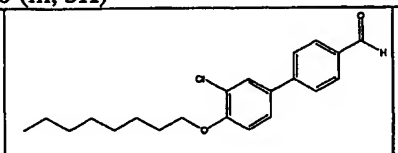
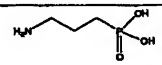
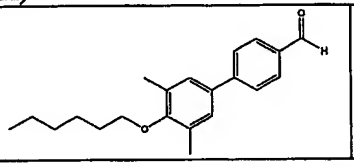
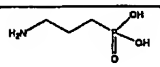
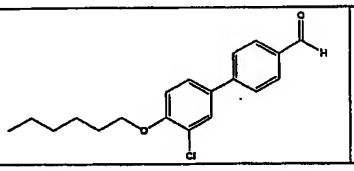
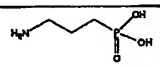
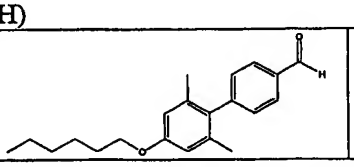
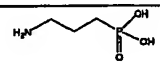
61			426.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.56 (s, 1H), 4.13 (s, 2H), 4.02-4.04 (m, 2H), 3.13-3.12 (m, 2H), 1.98-2.00 (m, 2H), 1.75-1.84 (m, 4H), 1.49-1.58 (m, 2H), 1.26-1.42 (m, 8H), 0.89-0.91 (m, 3H)			
62			386.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.14 (s, 2H), 4.08 (s, 2H), 3.79 (t, J=6.4 Hz, 2H), 3.13 (t, J=7.6 Hz, 2H), 2.30 (s, 6H), 1.95-2.05 (m, 2H), 1.76-1.84 (m, 4H), 1.51-1.58 (m, 2H), 1.31-1.44 (m, 8H), 0.90-0.95 (m, 3H)			
63			364.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.40 (d, J=8.7 Hz, 2H), 7.26 (t, J=7.26 Hz, 2H), 7.17-7.22 (m, 3H), 6.99 (d, J=8.7 Hz, 2H), 4.13 (s, 2H), 3.99 (t, J=6.2 Hz, 2H), 3.13 (t, J=7.6 Hz, 2H), 2.81 (t, J=7.6 Hz, 2H), 2.06-2.12 (m, 2H), 1.95-2.04 (m, 2H), 1.76-1.85 (m, 2H)			
64			255.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.7 Hz, 2H), 7.26 (t, J=7.5 Hz, 2H), 7.20 (d, J=7.1 Hz, 2H), 7.14-7.18 (m, 1H), 6.98 (d, J=8.7 Hz, 2H), 4.12 (s, 2H), 4.02 (s, 2H), 3.12 (t, J=7.4 Hz, 2H), 2.66-2.72 (m, 2H), 1.94-2.04 (m, 2H), 1.76-1.84 (m, 6H)			
65			399.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.60 (d, J=7.8 Hz, 2H), 7.49 (t, J=7.3 Hz, 2H), 4.26 (s, 2H), 3.19 (t, J=7.4 Hz, 3H), 3.09 (s, 2H), 2.96 (s, 2H), 1.98-2.08 (m, 2H), 1.78-1.86 (m, 2H), 1.22-1.32 (m, 4H), 1.00-1.04 (m, 8H)), 0.88-0.94 (m, 3H)			
66			514.0

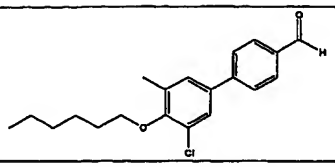
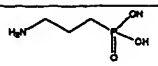
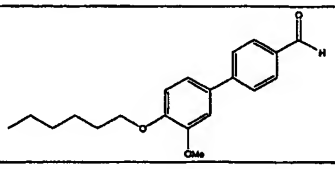
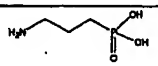
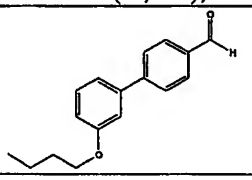
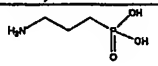
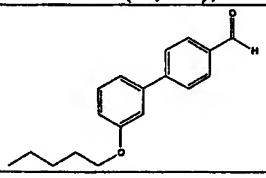
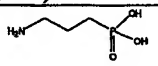
^{1}H NMR (500 MHz , CD_3OD) δ 7.51 (s, 2H), 7.18 (d, 2H), 4.12 (s, 2H), 3.99 (t, J=6.5 Hz, 2H), 3.90 (s, 3H), 3.15 (t, J=7.4 Hz, 2H), 1.96-2.06 (m, 2H), 1.75-1.84 (m, 4H), 1.50-1.56 (m, 2H), 1.29-1.41 (m, 8H), 0.89-0.95 (m, 3H)			
67			462.1
^{1}H NMR (500 MHz , CD_3OD) δ 6.99 (d, 2H), 4.14 (s, 2H), 3.97 (t, J=6.5 Hz, 2H), 3.89 (s, 3H), 3.15 (t, J=7.2 Hz, 2H), 2.93 (t, J=7.2 Hz, 2H), 1.96-2.06 (m, 2H), 1.66-1.84 (m, 6H), 1.48-1.56 (m, 2H), 1.28-1.42 (m, 8H), 1.04-1.10 (m, 3H), 0.90-0.96 (m, 3H)			
68			430.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.99 (s, 1H), 6.91 (s, 1H), 4.12 (s, 2H), 3.95 (t, J=6.4 Hz, 2H), 3.88 (s, 3H), 3.15 (t, J=7.4 Hz, 2H), 2.62 (t, J=7.8 Hz, 2H), 1.96-2.06 (m, 2H), 1.72-1.85 (m, 4H), 1.58-1.68 (m, 2H), 1.48-1.54 (m, 2H), 1.30-1.42 (m, 8H), 0.95-1.00 (m, 3H), 0.90-0.95 (m, 3H)			
69			386.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.10 (s, 1H), 7.00 (s, 2H), 4.12 (s, 2H), 4.02 (s, 2H), 3.89 (s, 3H), 3.10-3.16 (m, 2H), 1.94-2.04 (m, 2H), 1.73-1.83 (m, 4H), 1.62-1.71 (m, 2H), 1.26-1.52 (m, 8H), 0.88-0.96 (m, 3H)			
70			422.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.16 (s, 1H), 7.13 (s, 1H), 4.13 (s, 2H), 4.01 (t, J=6.6 Hz, 2H), 3.92 (s, 3H), 3.15 (t, J=7.2 Hz, 2H), 1.96-2.06 (m, 2H), 1.72-1.84 (m, 4H), 1.48-1.55 (m, 2H), 1.28-1.41 (m, 8H), 0.89-0.95 (m, 3H)			
71			482.3

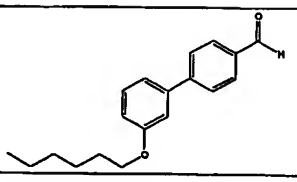
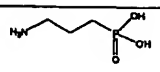
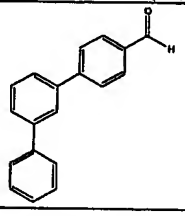
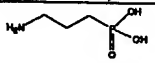
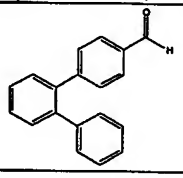
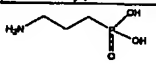
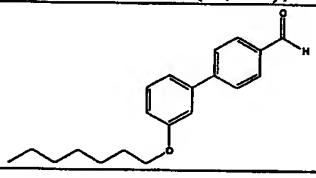
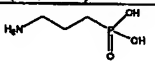
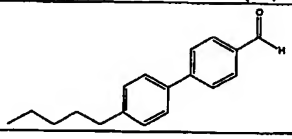
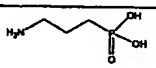
^{1}H NMR (500 MHz , CD_3OD) δ 7.32 (d, 1H), 7.17 (d, 1H), 4.15 (s, 2H), 4.01 (t, J=6.4 Hz, 2H), 3.92 (s, 3H), 3.17 (t, J=7.6 Hz, 2H), 1.98-2.08 (m, 2H), 1.74-1.87 (m, 4H), 1.49-1.59 (m, 2H), 1.28-1.44 (m, 10H), 0.90-0.96 (m, 3H)			
72			454.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.32 (d, 1H), 7.17 (d, 1H), 4.15 (s, 2H), 4.01 (t, J=6.5 Hz, 2H), 3.92 (s, 3H), 3.17 (t, J=7.5 Hz, 2H), 1.98-2.08 (m, 2H), 1.75-1.86 (m, 4H), 1.49-1.56 (m, 2H), 1.32-1.43 (m, 6H), 0.92-0.96 (m, 3H)			
73			544.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.49 (d, J=7.3 Hz, 2H), 7.41 (t, J=7.4 Hz, 2H), 7.37 (d, J=7.3 Hz, 1H), 7.33 (s, 1H), 7.25 (s, 1H), 5.18 (s, 2H), 4.13 (s, 2H), 4.02 (t, J=6.4 Hz, 2H), 3.12 (t, J=7.3 Hz, 2H), 1.96-2.06 (m, 2H), 1.70-1.84 (m, 4H), 1.40-1.48 (m, 2H), 1.22-1.36 (m, 8H), 0.88-0.94 (m, 3H)			
74			464.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.47 (d, J=7.5 Hz, 2H), 7.38 (t, J=7.4 Hz, 2H), 7.33 (d, J=7.4 Hz, 1H), 7.15 (s, 1H), 7.04 (s, 2H), 5.16 (s, 2H), 4.09 (s, 2H), 4.05 (t, J=6.3 Hz, 2H), 3.08 (t, J=7.4 Hz, 2H), 1.93-2.04 (m, 2H), 1.73-1.84 (m, 4H), 1.47-1.55 (m, 8H), 1.26-1.41 (m, 8H), 0.88-0.93 (m, 3H)			
75			350.1
^{1}H NMR (500 MHz , CD_3OD) δ 6.94-6.98 (m, 2H), 6.88-6.92 (m, 1H), 4.05 (s, 4H), 3.32 (s, 2H), 3.11 (t, J=7.2 Hz, 2H), 1.94-2.04 (m, 2H), 1.73-1.86 (m, 4H), 1.27-1.45 (m, 10H), 0.88-0.95 (m, 3H)			
76			496.2

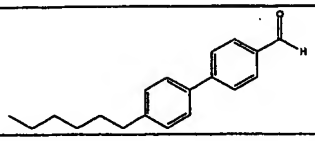
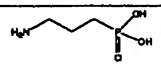
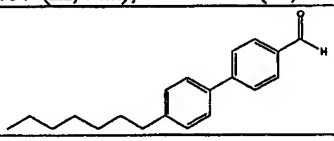
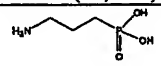
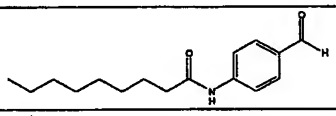
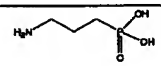
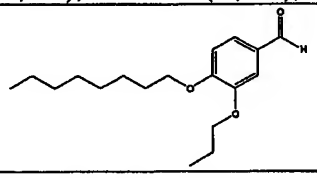
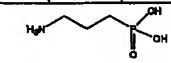
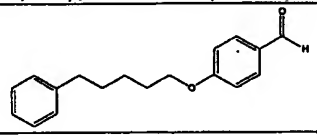
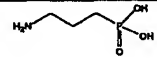
^{1}H NMR (500 MHz , CD_3OD) δ 7.31 (s, 1H), 7.18 (s, 1H), 4.12 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.92 (s, 3H), 3.15 (t, J=7.1 Hz, 2H), 1.96-2.06 (m, 2H), 1.73-1.82 (m, 4H), 1.49-1.56 (m, 2H), 1.27-1.42 (m, 12H), 0.89-0.94 (m, 3H)			
77			438.0
^{1}H NMR (500 MHz , CD_3OD) δ 7.31 (s, 1H), 7.18 (s, 1H), 4.12 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.92 (s, 3H), 3.12-3.17 (t, 2H), 1.96-2.06 (m, 2H), 1.73-1.82 (m, 4H), 1.48-1.57 (m, 2H), 1.34-1.41 (m, 4H), 0.91-0.97 (m, 3H)			
78			510.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.31 (s, 1H), 7.18 (s, 1H), 4.11 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.92 (s, 3H), 3.11-3.17 (t, 2H), 1.95-2.06 (m, 2H), 1.71-1.81 (m, 4H), 1.48-1.56 (m, 2H), 1.27-1.42 (m, 14H), 0.88-0.94 (m, 3H)			
79			302.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.31-7.40 (m, 2H), 7.02-7.08 (m, 2H), 4.12 (s, 2H), 4.03 (t, J=6.4 Hz, 2H), 3.12 (t, J=6.4 Hz, 2H), 1.94-2.04 (m, 2H), 1.66-1.81 (m, 4H), 1.48-1.56 (m, 2H), 0.97-1.02 (m, 3H)			
80			442.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.43 (d, J=7.5 Hz, 4H), 7.38 (t, J=7.5 Hz, 4H), 7.33 (d, J=7.1 Hz, 2H), 6.76 (s, 2H), 6.71 (s, 1H), 5.10 (s, 4H), 4.08 (s, 2H), 3.08 (t, J=6.4 Hz, 2H), 1.93-2.04 (m, 2H), 1.68-1.76 (m, 2H)			
81			402.2

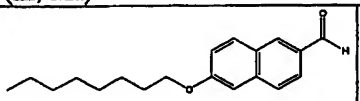
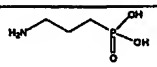
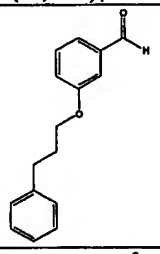
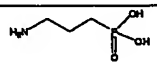
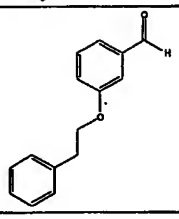
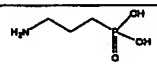
^{1}H NMR (500 MHz , CD_3OD) δ 6.98 (s, 1H), 6.90 (s, 1H), 4.10 (s, 2H), 3.94 (t, J=6.6 Hz, 2H), 3.88 (s, 3H), 3.14 (t, J=7.7 Hz, 2H), 2.27 (s, 3H), 1.96-2.06 (m, 2H), 1.71-1.85 (m, 4H), 1.46-1.54 (m, 2H), 1.28-1.42 (m, 8H), 0.90-0.95 (m, 3H)			
82			464.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.52 (d, J=7.4 Hz, 2H), 7.42 (t, J=7.4 Hz, 2H), 7.36 (t, J=7.3 Hz, 1H), 7.17 (s, 1H), 7.08 (s, 1H), 4.20 (s, 2H), 3.95 (s, 3H), 3.71 (t, J=6.3 Hz, 2H), 3.36 (s, 2H), 3.19 (t, J=7.5 Hz, 2H), 1.98-2.09 (m, 2H), 1.78-1.87 (m, 2H), 1.41-1.48 (m, 2H), 1.25-1.34 (m, 2H), 1.08-1.25 (m, 6H), 0.87-0.94 (m, 3H)			
83			374.2
^{1}H NMR (500 MHz , CD_3OD) δ 6.94-6.98 (m, 2H), 6.88-6.92 (m, 1H), 4.05 (s, 4H), 3.32 (s, 2H), 3.11 (t, J=7.2 Hz, 2H), 1.94-2.04 (m, 2H), 1.73-1.86 (m, 4H), 1.27-1.45 (m, 10H), 0.88-0.95 (m, 3H)			
84			392.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.69 (d, J=8.0, 2H), 7.57 (d, J=8.7 Hz, 2H), 7.54 (d, J=8.0 Hz, 2H), 7.01 (d, J=8.5 Hz, 2H), 4.22 (s, 2H), 4.03 (t, 2H), 3.18 (t, 2H), 1.98-2.08 (m, 2H), 1.76-1.86 (m, 4H), 1.40-1.53 (m, 4H), 0.96-1.00 (m, 3H)			
85			378.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.70 (d, J=8.3 Hz, 2H), 7.58 (d, J=8.7 Hz, 2H), 7.55 (d, J=7.55 Hz, 2H), 7.02 (d, J=8.7 Hz, 2H), 4.24 (s, 2H), 4.05 (t, J=6.4 Hz, 2H), 3.20 (t, J=7.6 Hz, 2H), 1.99-2.10 (m, 2H), 1.76-1.88 (m, 4H), 1.51-1.59 (m, 2H), 1.00-1.08 (m, 3H)			
86			406.2

^{1}H NMR (500 MHz , CD_3OD) δ 7.70 (d, J=8.3 Hz, 2H), 7.58 (d, J=8.7 Hz, 2H), 7.55 (d, J=8.3 Hz, 2H), 7.02 (d, J=8.4 Hz, 2H), 4.24 (s, 2H), 4.04 (t, J=6.4 Hz, 2H), 3.16-3.23 (t, 2H), 1.99-2.10 (m, 2H), 1.76-1.88 (m, 4H), 1.48-1.58 (m, 2H), 1.36-1.45 (m, 4H), 0.91-1.00 (m, 3H)			
87			468.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.69 (d, J=8.0 Hz, 2H), 7.67 (s, 1H), 7.56 (d, J=8.2 Hz, 2H), 7.15 (d, J=8.5 Hz, 2H), 4.24 (s, 2H), 4.11 (t, J=6.1 Hz, 2H), 3.19 (t, J=7.2 Hz, 2H), 1.98-2.08 (m, 2H), 1.78-1.88 (m, 4H), 1.51-1.59 (m, 2H), 1.29-1.46 (m, 8H), 0.88-0.96 (m, 3H)			
88			434.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.68 (d, J=8.2 Hz, 2H), 7.54 (d, J=8.2 Hz, 2H), 7.30 (s, 2H), 4.24 (s, 2H), 3.83 (t, J=6.5 Hz, 2H), 3.19 (t, J=7.4 Hz, 2H), 2.34 (s, 6H), 2.00-2.09 (m, 2H), 1.78-1.88 (m, 4H), 1.54-1.62 (m, 2H), 1.38-1.46 (m, 4H), 0.94-1.01 (m, 3H)			
89			440.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.70 (d, J=8.0 Hz, 2H), 7.68 (s, 1H), 7.57 (d, J=8.0 Hz, 3H), 7.16 (d, J=8.5 Hz, 1H), 4.25 (s, 2H), 4.12 (t, J=6.3 Hz, 2H), 3.20 (t, J=7.5 Hz, 2H), 2.00-2.09 (m, 2H), 1.80-1.90 (m, 4H), 1.53-1.61 (m, 2H), 1.38-1.46 (m, 4H), 0.93-0.99 (m, 3H)			
90			
^{1}H NMR (500 MHz , CD_3OD) δ 7.57 (d, J=8.0 Hz, 2H), 7.24 (d, J=7.8 Hz, 2H), 6.67 (s, 2H), 4.25 (s, 2H), 3.94-4.00 (t, 2H), 3.18-3.25 (t, 2H), 2.00-2.05 (m, 2H), 1.99 (s, 6H), 1.78-1.90 (m, 4H), 1.45-1.55 (m, 2H), 1.35-1.40 (m, 4H), 0.95-1.00 (m, 3H)			

91			454.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.68 (d, J=8.0 Hz, 2H), 7.57 (d, J=7.57, 2H), 7.51 (s, 1H), 7.43 (s, 1H), 4.22 (s, 2H), 3.97 (t, J=6.3 Hz, 2H), 3.14-3.22 (t, 2H), 2.38 (s, 3H), 1.98-2.08 (m, 2H), 1.74-1.88 (m, 4H), 1.54-1.62 (m, 2H), 1.36-1.46 (m, 4H), 0.92-1.00 (m, 3H)			
92			436.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.71 (d, J=8.0 Hz, 2H), 7.54 (d, J=8.3 Hz, 2H), 7.20-7.23 (m, 1H), 7.18-7.20 (m, 1H), 7.04 (d, J=8.5 Hz, 1H), 4.24 (s, 2H), 4.05 (t, J=6.5 Hz, 2H), 3.92 (s, 3H), 3.19 (t, J=7.4 Hz, 2H), 2.00-2.08 (m, 2H), 1.78-1.88 (m, 4H), 1.48-1.56 (m, 2H), 1.36-1.43 (m, 4H), 0.92-0.98 (m, 3H)			
93			
^{1}H NMR (500 MHz , CD_3OD) δ 7.71 (d, J=8.1 Hz, 2H), 7.57 (d, J=7.5 Hz, 2H), 7.32-7.39 (m, 1H), 7.10-7.21 (m, 2H), 6.90-6.96 (m, 1H), 4.16-4.25 (m, 2H), 4.00-4.08 (m, 2H), 3.12-3.22 (m, 2H), 1.96-2.06 (m, 2H), 1.72-1.84 (m, 2H), 1.62-1.72 (m, 2H), 1.50-1.60 (m, 2H), 1.38-1.48 (m, 2H), 0.98-1.06 (m, 3H)			
94			302.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.69-7.74 (m, 2H), 7.57 (d, J=7.6 Hz, 2H), 7.32-7.39 (m, 1H), 7.19 (d, J=7.1 Hz, 1H), 7.15 (s, 1H), 6.94 (d, J=8.0 Hz, 1H), 4.25 (s, 2H), 4.03-4.05 (m, 2H), 3.18-3.21 (m, 2H), 1.97-2.09 (m, 2H), 1.76-1.88 (m, 4H), 1.46-1.54 (m, 2H), 1.38-1.46 (m, 2H), 0.94-1.00 (m, 3H)			

95			406.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.73 (d, J=8.3 Hz, 2H), 7.58 (d, J=8.2 Hz, 2H), 7.38 (t, J=7.9 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 7.16 (s, 1H), 6.90 (d, J=6.0 Hz, 1H), 4.26 (s, 2H), 4.05 (t, J=6.4 Hz, 2H), 3.21 (t, J=7.5 Hz, 2H), 2.00-2.10 (m, 2H), 1.78-1.88 (m, 4H), 1.50-1.56 (m,, 2H), 1.36-1.44 (m, 4H), 0.92-0.98 (m, 3H)			
96			382.0
^{1}H NMR (500 MHz , CD_3OD) δ 7.87 (s, 1H), 7.82 (d, J=7.7 Hz, 2H), 7.69 (d, J=7.8 Hz, 2H), 7.59-7.67 (m, 4H), 7.54-7.59 (m, 1H), 7.49 (t, J=7.6 Hz, 2H), 7.36-7.42 (m, 1H), 4.29 (s, 2H), 3.22 (t, J=7.6 Hz, 2H), 2.00-2.12 (m, 2H), 1.80-1.90 (m, 2H)			
97			382.0
^{1}H NMR (500 MHz , CD_3OD) δ 7.45-7.48 (m, 2H), 7.40-7.45 (m, 2H), 7.36 (d, J=8.1 Hz, 2H), 7.25 (d, J=8.3 Hz, 2H), 7.18-7.22 (m, 3H), 7.11-7.15 (m, 2H), 4.17 (s, 2H), 3.14 (t, J=7.6 Hz, 2H), 1.99-2.01 (m, 2H), 1.95-1.97 (m, 2H)			
98			420.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.72 (d, J=8.0 Hz, 2H), 7.57 (d, J=8.0 Hz, 2H), 7.34-7.39 (t, 1H), 7.18-7.22 (d, 1H), 7.15 (s, 1H), 6.92-6.96 (d, 1H), 4.25 (s, 2H), 4.04 (t, J=6.4 Hz, 2H), 3.19 (t, J=7.5 Hz, 2H), 1.98-2.08 (m, 2H), 1.76-1.86 (m, 4H), 1.47-1.55 (m, 2H), 1.31-1.45 (m, 6H), 0.90-0.96 (m, 3H)			
99			376.2

^{1}H NMR (500 MHz , CD_3OD) δ 7.72 (d, J=8.3 Hz, 2H), 7.56 (d, J=8.0 Hz, 4H), 7.29 (d, J=8.0 Hz, 2H), 4.24 (s, 2H), 3.19 (t, J=7.6 Hz, 2H), 2.66 (t, J=7.6 Hz, 2H), 2.00-2.09 (m, 2H), 1.79-1.87 (m, 2H), 1.63-1.70 (m, 2H), 1.28-1.41 (m, 4H), 0.89-0.96 (m, 3H)			
100			390.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.72 (d, J=8.0 Hz, 2H), 7.56 (d, J=7.8 Hz, 4H), 7.29 (d, J=8.0 Hz, 2H), 4.25 (s, 2H), 3.19 (t, J=7.5 Ha, 2H), 2.67 (t, J=7.7, 2H), 2.00-2.09 (m, 2H), 1.78-1.87 (m, 2H), 1.61-1.70 (m, 2H), 1.31-1.41 (m, 6H), 0.98-0.94 (m, 3H)			
101			404.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.73 (d, J=8.0 Hz, 2H), 7.57 (d, J=7.6 Hz, 2H), 7.30 (d, J=8.3 Hz, 4H), 4.26 (s, 2H), 3.20 (t, J=7.6 Hz, 2H), 2.68 (t, J=7.7 Hz, 2H), 2.00-2.10 (m, 2H0, 1.80-1.88 (m, 2H), 1.64-1.70 (m, 2H), 1.26-1.40 (m, 8H), 0.90-0.95 (m, 3H)			
102			330.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.37 (t, J=8.0 Hz, 1H), 6.99-7.07 (m, 3H), 4.16 (s, 2H), 4.02 (t, J=6.6 Hz, 2H), 3.15 (t, J=7.6 Hz, 2H), 1.96-2.06 (m, 2H), 1.75-1.84 (m, 4H), 1.46-1.54 (m, 2H), 1.34-1.46 (m, 8H), 0.91-0.97 (m, 3H)			
103			416.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.07 (s, 1H), 6.99 (s, 2H), 4.09 (s, 2H), 4.03 (t, J=6.3 Hz, 2H), 3.97 (t, J=6.3 Hz, 2H), 3.11 (J=7.1 Hz, 2H), 1.93-2.04 (m, 2H), 1.72-1.84 (m, 6H), 1.46-1.54 (m, 2H), 1.26-1.42 (m, 8H), 1.02-1.08 (m, 3H), 0.86-0.94 (m, 3H)			
104			392.2

^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.4 Hz, 2H), 7.25 (t, J=7.5 Hz, 2H), 7.12-7.19 (m, 3H), 6.98 (d, J=8.7 Hz, 2H), 4.12 (s, 2H), 4.00 (t, J=6.4 Hz, 2H), 3.13 (t, J=7.5 Hz, 2H), 2.65 (t, J=7.6 Hz, 2H), 1.94 (m, 2H), 1.74-1.86 (m, 4H), 1.66-1.74 (m, 2H), 1.48-1.56 (m, 2H)			
105			408.4
^{1}H NMR (500 MHz , CD_3OD) δ 7.91 (s, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.82 (d, J=8.9 Hz, 1H), 7.51 (d, J=8.5 Hz, 1H), 7.27 (s, 1H), 7.21 (d, J=8.8 Hz, 1H), 4.32 (s, 2H), 4.11 (t, J=6.3 Hz, 2H), 3.16-3.22 (m, 2H), 1.98-2.08 (m, 2H), 1.76-1.90 (m, 4H), 1.48-1.58 (m, 2H), 1.28-1.46 (m, 8H), 0.90-0.96 (m, 3H)			
106			440.4
107			426.3
^{1}H NMR (500 MHz , CD_3OD) δ 7.71 (d, J=7.8 Hz, 2H), 7.56 (d, J=8.0, 2H), 7.28-7.39 (m, 5H), 7.18-7.25 (m, 2H), 7.14 (s, 1H), 6.95 (d, J=8.0 Hz, 1H), 4.22-4.31 (m, 4H), 3.19 (d, J=7.4 Hz, 2H), 3.11 (d, J=6.6 Hz, 2H), 1.97-2.09 (m, 2H), 1.78-1.88 (m, 2H)			

EXAMPLE 108

(R/S)-3-(N-(4-Nonylbenzyl)amino-1-hydroxypropylphosphonic acid

Step A: (R/S)-Diethyl 3-benzyloxycarbonylamino-1-hydroxypropylphosphonate

To a solution of potassium bis(trimethylsilyl)amide (1.13g, 5.66 mmol) in tetrahydrofuran (10 mL) at 0 °C was added diethyl phosphite (0.73 g, 5.66 mmol). After 10 min, 3-(benzyloxycarbonylamino)propanal (0.78 g, 3.77 mmol) was added as a solution in tetrahydrofuran (5 mL). After 30 min, the reaction was quenched by the addition of 2N hydrochloric acid (25 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with sat'd sodium chloride (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. Silica gel chromatography eluting with hexane/acetone (1:1) gave a colorless oil (0.36 g): ESI-MS 346.1 (M+H).

Step B: (R/S)-Diethyl 3-amino-1-hydroxypropylphosphonate

(R/S)-Diethyl 3-benzyloxycarbonylamino-1-hydroxypropylphosphonate (0.36 g, 1.04 mmol, from Step A) and palladium on carbon (10%, 0.10 g) were stirred together in methanol (5 mL) under an atmosphere of hydrogen. After 2 h, the reaction was filtered and concentrated *in vacuo* to give a colorless oil: ^{1}H NMR (500 MHz , CD_3OD) δ 4.10-4.22 (m, 4H), 4.00-4.05 (m, 1H), 2.85-3.00 (m, 2H), 1.85-2.00 (m, 2H), 1.34 (t, J=7.0 Hz, 6H); ESI-MS 211.8 (M+H)

Step: C (R/S)-Diethyl 3-(N-(4-nonylbenzyl)amino-1-hydroxypropylphosphonate

(R/S)-Diethyl 3-amino-1-hydroxypropylphosphonate (0.030 g, 0.142 mmol, from Step C), 4-nonylbenzaldehyde (0.036 g, 0.142 mmol) and sodium cyanoborohydride (0.004 g, 0.071 mmol) in methanol (1.5 mL) were heated at 50°C for 3 h. The reaction was made acidic (pH~5) by the addition of concentrated hydrochloric acid then directly purified by LC-3 to give a colorless oil (0.031 g).

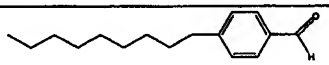
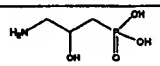
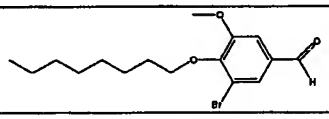
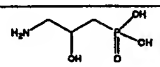
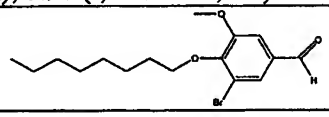
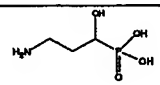
Step D: (R/S)-3-(N-(4-nonylbenzyl)amino-1-hydroxypropylphosphonic acid

(R/S)-Diethyl 3-(N-(4-nonylbenzyl)amino-1-hydroxypropylphosphonate (0.031 g) was dissolved in acetonitrile (1 mL) and treated with bromotrimethylsilane (0.050 mL, 0.362 mmol). After stirring for 1 h at 50°C, the reaction was quenched with methanol (1 mL), stirred for 30 min then concentrated. The residue was purified via HPLC to give desired product (0.011 g): ^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.3 Hz, 2H), 7.28 (d, J=8.3 Hz, 2H), 4.16 (s, 2H), 3.87-3.92 (m, 1H), 3.18-3.34 (m,

2H), 2.64 (t, J=7.7 Hz, 2H), 2.04-2.20 (m, 2H), 1.58-1.64 (m, 2H), 1.24-1.34 (m, 12H), 0.89 (t, J=7.0 Hz, 3H); ESI-MS 372.2 (M+H).

EXAMPLES 109-111

The following EXAMPLES (109-111) were made according to the procedure described for EXAMPLE 108 substituting A for 4-nonylbenzaldehyde and the diethyl ester of B for (R/S)-diethyl 3-amino-1-hydroxyphosphonate in Step C.

EXAMPLE	A	B	ESI-MS
109			372.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.42 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 4.24-4.50 (m, 1H), 4.21 (s, 2H), 3.30-3.38 (m, 1H), 3.01 (dd, J=12.8, 9.6 Hz, 1H), 2.67 (t, J=7.7 Hz, 2H), 1.94-2.14 (m, 2H), 1.60-1.68 (m, 2H), 1.26-1.38 (m, 12H), 0.92 (t, J=7.0 Hz, 3H)			
110			482.2
^{1}H NMR (500 MHz , CD_3OD) δ 7.33 (d, J=1.9 Hz, 1H), 7.19 (d, J=1.8 Hz, 1H), 4.22-4.28 (m, 1H), 4.18 (s, 2H), 4.01 (t, J=6.4 Hz, 2H), 3.93 (s, 3H), 3.30-3.35 (m, 1H), 3.03 (dd, J=12.6, 8.7 Hz, 1H), 1.91-2.11 (m, 2H), 1.75-1.82 (m, 2H), 1.50-1.58 (m, 2H), 1.30-1.42 (m, 8H), 0.93 (t, J=7.0 Hz, 3H)			
111			482.1
^{1}H NMR (500 MHz , CD_3OD) δ 7.33 (d, J=2.1 Hz, 1H), 7.19 (d, J=1.8 Hz, 1H), 4.18 (s, 2H), 4.02 (t, J=6.4 Hz, 2H), 3.92-3.96 (m, 1H), 3.93 (s, 3H), 3.23-3.36 (m, 2H), 2.08-2.26 (m, 2H), 1.75-1.82 (m, 2H), 1.50-1.58 (m, 2H), 1.30-1.42 (m, 8H), 0.93 (t, J=7.0 Hz, 3H)			

EXAMPLE 112

N-(4-Nonylbenzyl)-3-aminopropylphosphonic acid

3-Aminopropylphosphonic acid (0.060 g, 0.436 mmol) and tetrabutylammonium hydroxide (1.0M in methanol, 0.44 mL, 0.43 mmol) in methanol (3 mL) were heated at 50°C for 15 min until all of the solids had dissolved. 4-

(Nonyl)benzyliodide (0.100 g, 0.291 mmol) and DIEA (0.112 g, 0.872 mmol) were added and stirring was continued for 12 h at 50 °C. The reaction was made acidic (pH~5) by the addition of concentrated hydrochloric acid then directly purified using LC-3 to give the title compound (0.020 g): ^{1}H NMR (500 MHz , CD_3OD) δ 7.39 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 4.15 (s, 2H), 3.14 (t, J=7.6 Hz, 2H), 2.64 (t, J=7.7 Hz, 2H), 2.00 (m, 2H), 1.79 (td, J=5.3, 18.5 Hz, 2H), 1.61 (m, 2H), 1.24-1.36 (m, 14H), 0.89 (t, J=7.0 Hz, 3H); ESI-MS 356.2 (M+H).

EXAMPLE 113

3-[(4-Octylbenzyl)amino]propylphosphinic acid

Step A: Ethyl 2-cyanoethyl(diethoxymethyl)phosphinate

To a solution 2.6234 g (13.37 mmol) of ethyldiethoxymethyl phosphinate in 10 mL EtOH was added 0.5670 g (10.70 mmol) acrylonitrile. The resulting mixture was added to a solution of 0.071 g (2.81 mmol) NaH in 10 mL EtOH at 0 °C. The ice bath was removed at the end of the addition, and the reaction mixture was stirred at rt for 16 hr. The mixture was neutralized (pH = 7) with HOAc, and was partitioned between EtOAc and H_2O. The organic layer was separated, dried and concentrated, which provided 2.47 g (93% yield) of the title compound: ^{1}H NMR (500 MHz) δ 1.25 (t, J = 6.9, 6H), 1.34 (t, J = 7.1, 3H), 2.11-2.19 (m, 2H), 2.68-2.74 (m, 2H), 3.62-3.73 (m, 2H), 3.80-3.87 (m, 2H), 4.13-4.25 (m, 2H), 4.70 (d, J = 6.4, 1H); ESI-MS 250 (M+H).

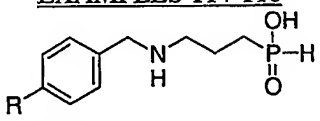
Step B: Ethyl 3-Aminopropyl(diethoxymethyl)phosphinate

To a solution of 2.47 g (9.91 mmol) of ethyl 2-cyanoethyl (diethoxymethyl)phosphinate (from Step A) in 20 mL 2.0 M ammonia in EtOH was added 250 mg Raney Nickel. The mixture was subjected to hydrogenation conditions (H_2, 40 psi, rt) for 16 hr. The reaction mixture was filtered over Celite and partitioned between CH_2Cl_2 and H_2O. The aqueous phase was extracted twice with CH_2CL_2. The organic layer and extractions were combined, dried, and concentrated to provide 2.13 g (85% yield) of the title compound: ^{1}H NMR (500 MHz) δ 1.23 (dt, J_1 = 7.1, J_2 = 1.6 6H), 1.29 (t, J = 7.1, 3H), 1.42 (s, br, 2H), 1.71-1.82 (m, 4H), 2.72-2.75 (m, 2H), 3.63-3.70 (m, 2H), 3.78-3.86 (m, 2H), 4.08-4.21 (m, 2H), 4.64 (d, J = 6.7, 1H); ESI-MS 254 (M+H).

Step C: 3-[(4-Octylbenzyl)amino]propylphosphinic acid

A mixture of 98.5 mg (0.389 mmol) of ethyl 3-aminopropyl (diethoxymethyl)phosphinate (from Step B) and 84.9 mg (0.389 mmol) of 4-octylbenzaldehyde in 1 mL of MeOH at rt was treated with 12.2 mg (0.194 mmol) $Na(CN)BH_3$. The resulting reaction mixture was stirred at rt for 16 hr. The reaction was quenched with 0.5 mL of 12 N HCl, then heated up to 80 °C for 1 hr. The mixture was cooled and concentrated. HPLC purification (LC-2) afforded 60 mg (47%) of the title compound: ^{1}H NMR (500 MHz, CD_3OD) δ 0.88 (t, J = 7.1, 3H), 1.25-1.33 (m, 10H), 1.59-1.66 (m, 4H), 1.90-1.96 (m, 2H), 2.63 (t, J = 7.7, 2H), 3.09 (t, J = 6.9, 2H), 4.12 (s, 2H), 7.03 (d, J = 505.6, 1H), 7.27 (d, J = 8.0, 2H), 7.38 (d, J = 8.0, 2H); LC-1: 3.02 min; ESI-MS 326 (M+H).

EXAMPLES 114-116



The following compounds were prepared using procedures analogous to those described in EXAMPLE 113 substituting the appropriate Aldehyde for 4-octylbenzaldehyde in Step C.

EXAMPLE	R	LC-1 (min)	ESI-MS (M+H)
114	$CH_3(CH_2)_8$-	3.00	340
115	$CH_3(CH_2)_8O$-	2.93	356
116	$CH_3(CH_2)_9$-	3.23	354

EXAMPLE 117

3-(N-(4-(4'-Pentyl)biphenylmethyl))aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 56 for 4-octylbenzaldehyde in Step C: LC-1: 2.86 min; ESI-MS 360 (M+H).

EXAMPLE 118

3-(N-(4-(4'-Heptyloxy)biphenylmethyl))aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 51 for 4-octylbenzaldehyde in Step C: LC-1: 3.06 min; ESI-MS 404 (M+H).

EXAMPLE 119

3-N-(3-Bromo-5-methoxy-4-(octyloxy)benzyl)aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 13 for 4-octylbenzaldehyde in Step C: LC-1: 2.98 min; ESI-MS 450 (M+H).

EXAMPLE 120

3-N-(3-Fluoro-4-(nonyloxy)benzyl)aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting 3-fluoro-4-(nonyloxy)benzaldehyde for 4-octylbenzaldehyde in Step C: ^{1}H NMR (500 Mhz) δ 0.91 (t, J=7.0, 3H), 1.30-1.40 (m, 10H), 1.48-1.51 (m, 2H), 1.71-1.99 (m, 6H), 3.11 (t, J=7.2, 2H), 4.07 (t, J=6.4, 2H), 4.12 (s, 2H), 7.06 (d, J=519, 1H), 7.13-7.29 (m, 3H); LC-1: 2.96 min; ESI-MS 374 (M+H).

EXAMPLE 121

3-N-(2-Chloro-4-(nonyloxy)benzyl)aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting 2-chloro-4-(nonyloxy)benzaldehyde for 4-octylbenzaldehyde in Step C: LC-1 : 3.07 min; ESI-MS 390 (M+H).

EXAMPLE 122

3-N-(6-Heptyloxy)napthylmethyl)aminopropylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting 6-heptyloxy-1-napthaldehyde for 4-octylbenzaldehyde in Step C: LC-1: 2.90 min; ESI-MS 378 (M+H).

EXAMPLE 123

3-(N-(3-Cyclopropyloxy-4-(nonyloxy)benzyl)amino)propylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 77 for 4-octylbenzaldehyde in Step C: LC-1: 3.04 min; ESI-MS 412 (M+H).

EXAMPLE 124

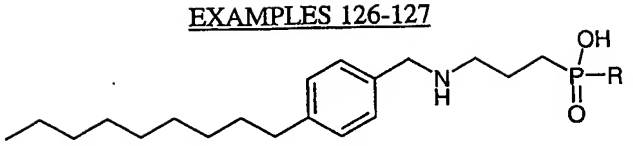
3-(N-(4-(Nonylthio)benzyl)amino)propylphosphinic acid

The title compound was using a procedure analogous to that described in EXAMPLE 113, substituting Aldehyde 78 for 4-octylbenzaldehyde in Step C: ^{1}H NMR (500 Mhz) (CD_3OD) δ 0.90 (t, J = 7.0, 3H), 1.30-1.32 (m, 10H), 1.43-1.46 (m, 2H), 1.63-1.66 (m, 2H), 1.78-1.83 (m, 2H), 1.95-1.99 (m, 2H), 2.98 (t, J = 7.2, 2H), 3.14 (t, J = 7.5, 2H), 4.16 (s, 2H), 7.08 (d, J = 533, 1H), 7.37-7.42 (m, 4H); LC-1: 3.10 min; ESI-MS 372 (M+H).

EXAMPLE 125

Ethyl (3-(4-nonylbenzyl)amino)propylphosphinic acid A solution of 88 mg (0.26 mmol) of 3-((4-nonylbenzyl)amino)propylphosphinic acid (from EXAMPLE 114) in 1 mL N,N-bis(trimethylsilyl)amine was heated to 100 °C for 8 hr. Upon cooling to rt, 81.1 mg (0.52 mmol) of iodoethane was added, followed by the addition of 67.2 mg (0.52 mmol) of DIEA. The resulting mixture was heated to 60 °C overnight. The reaction mixture was cooled and concentrated. HPLC purification (LC-2) afforded 12 mg (13%) of the title compound. ^{1}H NMR (500 MHz) (CD_3OD) δ 0.88 (t, J = 7.1, 3H), 1.09-1.18 (m, 3H), 1.26-1.31 (m, 12H), 1.59-1.75 (m, 6H), 1.94-2.00 (m, 2H), 2.63 (t, J = 7.6, 2H), 3.10 (t, J = 6.9, 2H), 4.13 (s, 2H), 7.27 (d, J = 8.0, 2H), 7.39 (d, J = 8.0 2H); LC-1: 2.92 min; ESI-MS 368 (M+H).

EXAMPLES 126-127



The following compounds were prepared a procedure analogous to that described in EXAMPLE 125 substituting the appropriate alkyl halide for ethyl iodide.

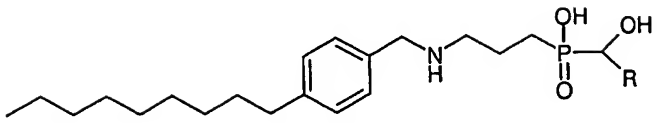
EXAMPLE	R	LC-1 (min)	ESI-MS (M+H)
126	$CH_3CH_2CH_2$-	3.03	382
127	$PhCH_2$-	3.41	430

EXAMPLE 128

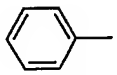
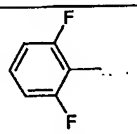
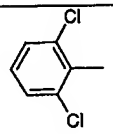
Hydroxymethyl (3-(4-nonylbenzyl)amino)propylphosphinic acid

A solution of 71 mg (0.21 mmol) of 3-(4-nonylbenzyl)aminopropylphosphinic acid (from EXAMPLE 114) in 1 mL of N,N-(trimethylsilyl)amine was heated to 100 °C for 8 hr. Upon cooling to rt, 15.8 mg (0.53 mmol) of paraformaldehyde was added. The resulting mixture was heated at 30 °C for 3 hr, and stirred at rt under nitrogen for 16 hr. The reaction mixture concentrated. HPLC purification (LC-2) afforded 22 mg (28%) of the title compound. ^{1}H NMR (500 MHz) (CD_3OD) δ 0.88 (t, J = 7.1, 3H), 1.27-1.31 (m, 12H), 1.57-1.63 (m, 2H), 1.80-1.85 (m, 2H), 1.97-2.05 (m, 2H), 2.63 (t, J = 7.8, 2H), 3.12 (t, J = 6.9, 2H), 3.70 (d, J = 6.2, 2H), 4.13 (s, 2H), 7.27 (d, J = 8.0, 2H), 7.39 (d, J = 8.2, 2H); LC-1: 2.90 min; ESI-MS 370 (M+H).

EXAMPLES 129-133



The following compounds were prepared using a procedure analogous to that described in EXAMPLE 128 substituting the appropriate aldehyde for paraformaldehyde.

EXAMPLE	R	LC-1 (min)	ESI-MS (M+H)
129	CH_3-	2.89	384
130	CH_3CH_2-	2.95	398
131		3.26	446
132		3.25	482
133		3.45	514

EXAMPLE 134

Hydroxymethyl (3-(4-octylbenzyl)amino)propylphosphinic acid

The title compound was prepared from 3-(4-octylbenzyl)aminopropylphosphinic acid (from EXAMPLE 114) using a procedure analogous to that described in EXAMPLE 128: LC-1: 2.67 min; ESI-MS 356 (M+H).

EXAMPLE 135

Hydroxymethyl 3-(3-(cyclopropyloxy)-4-(nonyloxy)benzyl)aminopropylphosphinic acid

The title compound was prepared from 3-(3-(cyclopropyloxy)-4-(nonyloxy)benzyl)aminopropylphosphinic acid (from EXAMPLE 123) using a procedure analogous to that described in EXAMPLE 128: LC-1: 2.95 min; ESI-MS 442 (M+H).

EXAMPLE 136

Hydroxymethyl 3-(3-fluoro-4-(nonyloxy)benzyl)aminopropylphosphinic acid

The title compound was prepared from 3-(3-fluoro-4-(nonyloxy)benzyl)amino-propylphosphinic acid (from EXAMPLE 125) using a procedure analogous to that described in EXAMPLE 128: LC-1: 2.87 min; ESI-MS 404 (M+H).

EXAMPLE 137

Ethoxycarbonyl 3-(N-(4-(4'-heptyloxy)biphenylmethyl))aminopropylphosphinic acid

To a solution of 32.5 mg (0.081 mmol) of 3-(N-(4-(4'-heptyloxy)biphenylmethyl)) aminopropylphosphinic acid (from EXAMPLE 118) in 2 mL dichloromethane was added 0.1 mL of TMSCl and 0.12 mL of DIEA at 0 °C. The solution was stirred at rt for an additional one hour and 0.1 mL of ethyl chloroformate (0.81 mmol) was added. The reaction was quenched with MeOH and concentrated to

oil. The product was isolated and purified by LC-2: ^{1}H NMR (500 Mhz) (CD_3OD) δ 0.94 (t, J = 6.9, 3H), 1.31-1.43 (m, 8H), 1.51-1.53 (m, 2H), 1.80-1.83 (m, 2H), 1.89-1.92 (m, 2H), 2.03-2.06 (m, 2H), 3.18 (t, J = 6.7, 2H), 4.05 (t, J = 6.4, 2H), 4.24 (s, 2H), 4.25 (q, J =7.0, 2H), 6.95-7.72 (m, 8H); LC-1: 3.26 min; ESI-MS 476 (M+H).

EXAMPLE 138

3-(4-Octylbenzyl)amino-2-phenylpropylphosphinic acid

A mixture of 69.2 mg (0.210 mmol) of ethyl 3-amino-2-phenylpropyl(diethoxymethyl)phosphinate (*Tetrahedron*, **1989**, 3787-3808) and 48.2 mg (0.221 mmol) of 4-octylbenzaldehyde in 1 mL of MeOH at rt was treated with 6.7 mg (0.105 mmol) of $Na(CN)BH_3$. The resulting reaction mixture was stirred at rt for 16 hr. The reaction was quenched with 0.3 mL of 12 N HCl, then heated up to 60 °C for 5 hr. The mixture was cooled and concentrated. HPLC purification (LC-2) afforded 22 mg (26%) of the title compound. ^{1}H NMR (500 MHz) (CD_3OD) δ 0.88 (t, J = 7.1, 3H), 1.26-1.30 (m, 10H), 1.58-1.61 (m, 2H), 2.01-2.17 (m, 2H), 2.62 (t, J = 7.8, 2H), 3.20-3.23 (m, 1H),3.35-3.46 (m, 2H), 4.11 (s, 2H), 6.92 (d, J = 525.4, 1H), 7.23-7.37 (m, 9H); LC-1: 3.31 min; ESI-MS 402 (M+H).

EXAMPLE 139

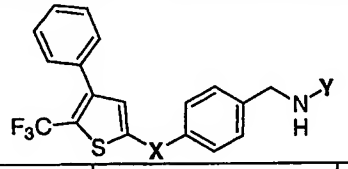
3-(3-Bromo-5-methoxy-4-(octyloxy)benzyl)amino-2-phenylpropylphosphinic acid

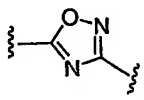
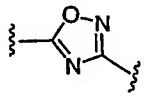
The title compound was prepared using a procedure analogous to that described in EXAMPLE 138 substituting Aldehyde 13 for 4-octylbenzaldehyde: LC-1: 3.51 min; ESI-MS 526 (M+H).

EXAMPLES 140-150

The following compounds were prepared using a procedure analogous to that described in EXAMPLE 1 substituting the appropriate aminoalkylcarboxylic acid or

aminoalkylphosphonic acid for 3-aminopropylphosphonic acid and either Aldehyde 79 or 80 for 4-(decyloxy)benzaldehyde. The products were purified using LC-2.



EXAMPLE	X	Y	LC-1 (min)	ESI-MS (M+H)
140		$-(CH_2)_3PO_3H_2$	3.01	524
141		$-(CH_2)_3CO_2H$	3.07	448
142	$-CH_2O-$	$-(CH_2)_3PO_3H_2$	2.77	486
143	$-CH_2O-$	$-(CH_2)_3CO_2H$	2.79	450
144	$-CH_2O-$	$-(CH_2)_2CO_2H$	2.72	436
145	$-CH_2O-$	$-CH_2CH(CH_3)CO_2H$	3.00	450
146	$-CH_2O-$	$-CH_2CH(OH)CO_2H$		
147	$-CH_2O-$	$-CH(n\text{-}Pr)CH_2CO_2H$	3.11	478

^{1}H NMR (500 MHz, CD_3OD) δ 0.97 (3H, t, J=7.3); 1.29-1.51 (2H, m); 1.63-1.71 (1H, m); 1.78-1.84 (1H, m); 2.66-2.83 (3H, m); 3.46-3.54 (1H, m); 4.23 (2H, s); 5.38 (2H, s); 7.12 (2H, d, J=8.5); 7.21 (1H, s); 7.41-7.44 (5H, m); 7.47 (2H, d, J=8.5)				
148	$-CH_2O-$	$-CH(i\text{-}Pr)CH_2CO_2H$	3.06	478
^{1}H NMR (500 MHz, CD_3OD) δ 0.97 (3H, d, J=6.8); 1.01 (3H, d, J=6.8); 2.15-2.21 (1H, m); 2.66-2.83 (3H, m); 3.48-3.51 (1H, m); 4.28 (2H, q, J=13 & 28); 5.39 (2H, s); 7.13 (2H, d, J=8.5); 7.21 (1H, s); 7.42-7.47 (5H, m); 7.49 (2H, d, J=8.5)				
149	$-CH_2O-$	$-CH(CH_3)CH_2CO_2H$	2.90	450
^{1}H NMR (500 MHz, CD_3OD) δ 1.42 (3H, d, J=6.6); 2.66-2.79 (2H, m); 2.83 (1H, s); 3.59-3.64 (1H, m); 4.21 (2H, q, J=13 & 28); 5.38 (2H, s); 7.13 (2H, d, J=8.4); 7.21 (1H, s); 7.42-7.45 (5H, m); 7.47 (2H, d, J=8.4)				
150	$-CH_2O-$	$-(CH_2)_4CO_2H$	2.95	464
^{1}H NMR (500 MHz, CD_3OD) δ 1.60-1.80 (4H, m); 2.30-2.50 (2H, m); 3.24 (2H, s); 4.53 (2H, s); 5.31 (2H, s); 7.13 (2H, d, J=8.4); 7.21 (1H, s); 7.42-7.45 (5H, m); 7.47 (2H, d, J=8.4)				

BIOLOGICAL ACTIVITY

The $S1P_1$/Edg1, $S1P_3$/Edg3, $S1P_2$/Edg5, $S1P_4$/Edg6 or $S1P_5$ /Edg8 activity of the compounds of the present invention can be evaluated using the following assays:

Ligand Binding to Edg/S1P Receptors Assay

^{33}P-sphingosine-1-phosphate was synthesized enzymatically from γ^{33}P-ATP and sphingosine using a crude yeast extract with sphingosine kinase activity in a reaction mix containing 50 mM KH_2PO_4, 1 mM mercaptoethanol, 1 mM

Na_3VO_4, 25 mM KF, 2 mM semicarbazide, 1 mM Na_2EDTA, 5 mM $MgCl_2$, 50 mM sphingosine, 0.1% TritonX-114, and 1 mCi γ^{33}P-ATP (NEN; specific activity 3000 Ci/mmol). Reaction products were extracted with butanol and ^{33}P-sphingosine-1-phosphate was purified by HPLC.

Cells expressing EDG/S1P receptors were harvested with enzyme-free dissociation solution (Specialty Media, Lavallette, NJ). They were washed once in cold PBS and suspended in binding assay buffer consisting of 50 mM HEPES-Na, pH 7.5, 5mM $MgCl_2$, 1mM $CaCl_2$, and 0.5% fatty acid-free BSA. ^{33}P-sphingosine-1-phosphate was sonicated with 0.1 nM sphingosine-1-phosphate in binding assay buffer; 100 µl of the ligand mixture was added to 100 µl cells (1 x 10^6 cells/mL) in a 96 well microtiter dish. Binding was performed for 60 min at room temperature with gentle mixing. Cells were then collected onto GF/B filter plates with a Packard Filtermate Universal Harvester. After drying the filter plates for 30 min, 40 µl of Microscint 20 was added to each well and binding was measured on a Wallac Microbeta Scintillation Counter. Non-specific binding was defined as the amount of radioactivity remaining in the presence of 0.5 µM cold sphingosine-1-phosphate.

Alternatively, ligand binding assays were performed on membranes prepared from cells expressing Edg/S1P receptors. Cells were harvested with enzyme-free dissociation solution and washed once in cold PBS. Cells were disrupted by homogenization in ice cold 20 mM HEPES pH 7.4, 10 mM EDTA using a Kinematica polytron (setting 5, for 10 seconds). Homogenates were centrifuged at 48,000 x g for 15 min at 4°C and the pellet was suspended in 20 mM HEPES pH 7.4, 0.1 mM EDTA. Following a second centrifugation, the final pellet was suspended in 20 mM HEPES pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$. Ligand binding assays were performed as described above, using 0.5 to 2 µg of membrane protein.

Agonists and antagonists of Edg/S1P receptors can be identified in the ^{33}P-sphingosine-1-phosphate binding assay. Compounds diluted in DMSO, methanol, or other solvent, were mixed with probe containing ^{33}P-sphingosine-1-phosphate and binding assay buffer in microtiter dishes. Membranes prepared from cells expressing Edg/S1P receptors were added, and binding to ^{33}P-sphingosine-1-phosphate was performed as described. Determination of the amount of binding in the presence of varying concentrations of compound and analysis of the data by non-linear regression software such as MRLCalc (Merck Research Laboratories) or PRISM (GraphPad Software) was used to measure the affinity of compounds for the

receptor. Selectivity of compounds for Edg/S1P receptors was determined by measuring the level of ^{33}P-sphingosine-1-phosphate binding in the presence of the compound using membranes prepared from cells transfected with each respective receptor ($S1P_1$/Edg1, $S1P_3$/Edg3, $S1P_2$/Edg5, $S1P_4$/Edg6, $S1P_5$/Edg8).

^{35}S-GTPγS Binding Assay

Functional coupling of S1P/Edg receptors to G proteins was measured in a ^{35}S-GTPγS binding assay. Membranes prepared as described in the Ligand Binding to Edg/S1P Receptors Assay (1-10 μg of membrane protein) were incubated in a 200 μl volume containing 20 mM HEPES pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$, 5 μM GDP; 0.1% fatty acid-free BSA (Sigma, catalog A8806), various concentrations of sphingosine-1-phosphate, and 125 pM ^{35}S-GTPγS (NEN; specific activity 1250 Ci/mmol) in 96 well microtiter dishes. Binding was performed for 1 hour at room temperature with gentle mixing, and terminated by harvesting the membranes onto GF/B filter plates with a Packard Filtermate Universal Harvester. After drying the filter plates for 30 min, 40 μl of Microscint 20 was added to each well and binding was measured on a Wallac Microbeta Scintillation Counter.

Agonists and antagonists of S1P/Edg receptors can be discriminated in the ^{35}S-GTPγS binding assay. Compounds diluted in DMSO, methanol, or other solvent, were added to microtiter dishes to provide final assay concentrations of 0.01 nM to 10 μM. Membranes prepared from cells expressing S1P/Edg receptors were added, and binding to ^{35}S-GTPγS was performed as described. When assayed in the absence of the natural ligand or other known agonist, compounds that stimulate ^{35}S-GTPγS binding above the endogenous level were considered agonists, while compounds that inhibit the endogenous level of ^{35}S-GTPγS binding were considered inverse agonists. Antagonists were detected in a ^{35}S-GTPγS binding assay in the presence of a sub-maximal level of natural ligand or known S1P/Edg receptor agonist, where the compounds reduced the level of ^{35}S-GTPγS binding. Determination of the amount of binding in the presence of varying concentrations of compound was used to measure the potency of compounds as agonists, inverse agonists, or antagonists of S1P/Edg receptors. To evaluate agonists, percent stimulation over basal was calculated as binding in the presence of compound divided by binding in the absence of ligand, multiplied by 100. Dose response curves were plotted using a non-linear regression curve fitting program MRLCalc (Merck Research Laboratories), and EC_{50} values were defined to be the concentration of agonist required to give 50% of its own

maximal stimulation. Selectivity of compounds for S1P/Edg receptors was determined by measuring the level of ^{35}S-GTPγS binding in the presence of compound using membranes prepared from cells transfected with each respective receptor.

Intracellular Calcium Flux Assay

Functional coupling of S1P/Edg receptors to G protein associated intracellular calcium mobilization was measured using FLIPR (Fluorescence Imaging Plate Reader, Molecular Devices). Cells expressing S1P/Edg receptors were harvested and washed once with assay buffer (Hanks Buffered Saline Solution (BRL) containing 20mM HEPES, 0.1% BSA and 710 μg/mL probenicid (Sigma)). Cells were labeled in the same buffer containing 500 nM of the calcium sensitive dye Fluo-4 (Molecular Probes) for 1 hour at 37°C and 5% CO_2. The cells were washed twice with buffer before plating $1.5x10^5$ per well (90μl) in 96 well polylysine coated black microtiter dishes. A 96-well ligand plate was prepared by diluting sphingosine-1-phosphate or other agonists into 200 μl of assay buffer to give a concentration that was 2-fold the final test concentration. The ligand plate and the cell plate were loaded into the FLIPR instrument for analysis. Plates were equilibrated to 37°C. The assay was initiated by transferring an equal volume of ligand to the cell plate and the calcium flux was recorded over a 3 min interval. Cellular response was quantitated as area (sum) or maximal peak height (max). Agonists were evaluated in the absence of natural ligand by dilution of compounds into the appropriate solvent and transfer to the Fluo-4 labeled cells. Antagonists were evaluated by pretreating Fluo-4 labeled cells with varying concentrations of compounds for 15 min prior to the initiation of calcium flux by addition of the natural ligand or other S1P/Edg receptor agonist.

Preparation of Cells Expressing S1P/Edg Receptors

Any of a variety of procedures may be used to clone $S1P_1$/Edg1, $S1P_3$/Edg3, $S1P_2$/Edg5, $S1P_4$/Edg6 or $S1P_5$/Edg8. These methods include, but are not limited to, (1) a RACE PCR cloning technique (Frohman, et al., 1988, *Proc. Natl. Acad. Sci. USA* 85: 8998-9002). 5′ and/or 3′ RACE may be performed to generate a full-length cDNA sequence; (2) direct functional expression of the Edg/S1P cDNA following the construction of an S1P/Edg-containing cDNA library in an appropriate expression vector system; (3) screening an S1P/Edg-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a labeled degenerate

oligonucleotide probe designed from the amino acid sequence of the S1P/Edg protein; (4) screening an S1P/Edg-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a partial cDNA encoding the S1P/Edg protein. This partial cDNA is obtained by the specific PCR amplification of S1P/Edg DNA fragments through the design of degenerate oligonucleotide primers from the amino acid sequence known for other proteins which are related to the S1P/Edg protein; (5) screening an S1P/Edg-containing cDNA library constructed in a bacteriophage or plasmid shuttle vector with a partial cDNA or oligonucleotide with homology to a mammalian S1P/Edg protein. This strategy may also involve using gene-specific oligonucleotide primers for PCR amplification of S1P/Edg cDNA; or (6) designing 5′ and 3′ gene specific oligonucleotides using the S1P/Edg nucleotide sequence as a template so that either the full-length cDNA may be generated by known RACE techniques, or a portion of the coding region may be generated by these same known RACE techniques to generate and isolate a portion of the coding region to use as a probe to screen one of numerous types of cDNA and/or genomic libraries in order to isolate a full-length version of the nucleotide sequence encoding S1P/Edg.

It is readily apparent to those skilled in the art that other types of libraries, as well as libraries constructed from other cell types-or species types, may be useful for isolating an S1P/Edg-encoding DNA or an S1P/Edg homologue. Other types of libraries include, but are not limited to, cDNA libraries derived from other cells.

It is readily apparent to those skilled in the art that suitable cDNA libraries may be prepared from cells or cell lines which have S1P/Edg activity. The selection of cells or cell lines for use in preparing a cDNA library to isolate a cDNA encoding S1P/Edg may be done by first measuring cell-associated S1P/Edg activity using any known assay available for such a purpose.

Preparation of cDNA libraries can be performed by standard techniques well known in the art. Well known cDNA library construction techniques can be found for example, in Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*; Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Complementary DNA libraries may also be obtained from numerous commercial sources, including but not limited to Clontech Laboratories, Inc. and Stratagene.

An expression vector containing DNA encoding an S1P/Edg-like protein may be used for expression of S1P/Edg in a recombinant host cell. Such recombinant host cells can be cultured under suitable conditions to produce S1P/Edg

or a biologically equivalent form. Expression vectors may include, but are not limited to, cloning vectors, modified cloning vectors, specifically designed plasmids or viruses. Commercially available mammalian expression vectors may be suitable for recombinant S1P/Edg expression.

Recombinant host cells may be prokaryotic or eukaryotic, including but not limited to, bacteria such as *E. coli*, fungal cells such as yeast, mammalian cells including, but not limited to, cell lines of bovine, porcine, monkey and rodent origin; and insect cells including but not limited to *Drosophila* and silkworm derived cell lines.

The nucleotide sequences for the various S1P/Edg receptors are known in the art. See, for example, the following:

S1P$_1$/Edg1 Human

Hla, T. and T. Maciag 1990 An abundant transcript induced in differentiating human endothelial cells encodes a polypeptide with structural similarities to G-protein coupled receptors. J. Biol Chem. 265:9308-9313, hereby incorporated by reference in its entirety.

WO91/15583, published on October 17, 1991, hereby incorporated by reference in its entirety.

WO99/46277, published on September 16, 1999, hereby incorporated by reference in its entirety.

S1P$_1$/Edg1 Mouse

WO0059529, published October 12, 2000, hereby incorporated by reference in its entirety.

U.S. No. 6,323,333, granted November 27, 2001, hereby incorporated by reference in its entirety.

S1P$_1$/Edg1 Rat

Lado, D.C., C. S. Browe, A.A. Gaskin, J. M. Borden, and A. J. MacLennan. 1994 Cloning of the rat edg-1 immediate-early gene: expression pattern suggests diverse functions. Gene 149: 331-336, hereby incorporated by reference in its entirety.

U.S. No. 5,585,476, granted December 17, 1996, hereby incorporated by reference in its entirety.

U.S. No. 5856,443, granted January 5, 1999, hereby incorporated by reference in its entirety.

S1P3/Edg3 Human

An, S., T. Bleu, W. Huang, O.G. Hallmark, S. R. Coughlin, E.J. Goetzl 1997 Identification of cDNAs encoding two G protein-coupled receptors for lysosphingolipids FEBS Lett. 417:279-282, hereby incorporated by reference in its entirety.

WO 99/60019, published November 25, 1999, hereby incorporated by reference in its entirety.

U.S. No. 6,130,067, granted October 10, 2000, hereby incorporated by reference in its entirety.

S1P3/Edg3 Mouse

WO 01/11022, published February 15, 2001, hereby incorporated by reference in its entirety.

S1P3/Edg3 Rat

WO 01/27137, published April 19, 2001, hereby incorporated by reference in its entirety.

S1P2/Edg5 Human

An, S., Y. Zheng, T. Bleu 2000 Sphingosine 1-Phosphate-induced cell proliferation, survival, and related signaling events mediated by G Protein-coupled receptors Edg3 and Edg5. J. Biol. Chem 275: 288-296, hereby incorporated by reference in its entirety.

WO 99/35259, published July 15, 1999, hereby incorporated by reference in its entirety.

WO99/54351, published October 28, 1999, hereby incorporated by reference in its entirety.

WO 00/56135, published September 28, 2000, hereby incorporated by reference in its entirety.

S1P2/Edg5 Mouse

WO 00/60056, published October 12, 2000, hereby incorporated by reference in its entirety.

S1P2/Edg5 Rat

Okazaki, H., N. Ishizaka, T. Sakurai, K. Kurokawa, K. Goto, M. Kumada, Y. Takuwa 1993 Molecular cloning of a novel putative G protein-coupled receptor expressed in the cardiovascular system. Biochem. Biophys. Res. Comm. 190:1104-1109, hereby incorporated by reference in its entirety.

MacLennan, A.J., C. S. Browe, A.A. Gaskin, D.C. Lado, G. Shaw 1994 Cloning and characterization of a putative G-protein coupled receptor potentially involved in development. Mol. Cell. Neurosci. 5: 201-209, hereby incorporated by reference in its entirety.

U.S. No. 5,585,476, granted December 17, 1996, hereby incorporated by reference in its entirety.

U.S. No. 5856,443, granted January 5, 1999, hereby incorporated by reference in its entirety.

S1P4/Edg6 Human

Graler, M.H., G. Bernhardt, M. Lipp 1998 EDG6, a novel G-protein-coupled receptor related to receptors for bioactive lysophospholipids, is specifically expressed in lymphoid tissue. Genomics 53: 164-169, hereby incorporated by reference in its entirety.

WO 98/48016, published October 29, 1998, hereby incorporated by reference in its entirety.

U.S. No. 5,912,144, granted June 15, 1999, hereby incorporated by reference in its entirety.

WO 98/50549, published November 12, 1998, hereby incorporated by reference in its entirety.

U.S. No. 6,060,272, granted May 9, 2000, hereby incorporated by reference in its entirety.

WO 99/35106, published July 15, 1999, hereby incorporated by reference in its entirety.

WO 00/15784, published March 23, 2000, hereby incorporated by reference in its entirety.

WO 00/14233, published March 16, 2000, hereby incorporated by reference in its entirety.

S1P4/Edg6 Mouse

WO 00/15784, published March 23, 2000, hereby incorporated by reference in its entirety.

S1P5/Edg8 Human

Im, D.-S., J. Clemens, T.L. Macdonald, K.R. Lynch 2001 Characterization of the human and mouse sphingosine 1-phosphate receptor, S1P5 (Edg-8): Structure-Activity relationship of sphingosine 1-phosphate receptors. Biochemistry 40:14053-14060, hereby incorporated by reference in its entirety.

WO 00/11166, published March 2, 2000, hereby incorporated by reference in its entirety.

WO 00/31258, published June 2, 2000, hereby incorporated by reference in its entirety.

WO 01/04139, published January 18, 2001, hereby incorporated by reference in its entirety.

EP 1 090 925, published April 11, 2001, hereby incorporated by reference in its entirety.

S1P5/Edg8 Rat

Im, D.-S., C.E. Heise, N. Ancellin, B. F. O'Dowd, G.-J. Shei, R. P. Heavens, M. R. Rigby, T. Hla, S. Mandala, G. McAllister, S.R. George, K.R. Lynch 2000 Characterization of a novel sphingosine 1-phosphate receptor, Edg-8. J. Biol. Chem. 275: 14281-14286, hereby incorporated by reference in its entirety.

WO 01/05829, published January 25, 2001, hereby incorporated by reference in its entirety.

Measurement of cardiovascular effects

The effects of compounds of the present invention on cardiovascular parameters can be evaluated by the following procedure:

Adult male rats (approx. 350 g body weight) were instrumented with femoral arterial and venous catheters for measurement of arterial pressure and intravenous compound administration, respectively. Animals were anesthetized with Nembutal (55 mg/kg, ip). Blood pressure and heart rate were recorded on the Gould Po-Ne-Mah data acquisition system. Heart rate was derived from the arterial pulse wave. Following an acclimation period, a baseline reading was taken (approximately 20 minutes) and the data averaged. Compound was administered intravenously (either bolus injection of approximately 5 seconds or infusion of 15 minutes duration), and data were recorded every 1 minute for 60 minutes post compound administration. Data are calculated as either the peak change in heart rate or mean arterial pressure or are calculated as the area under the curve for changes in heart rate or blood pressure versus time. Data are expressed as mean ± SEM. A one-tailed Student's paired t-test is used for statistical comparison to baseline values and considered significant at $p<0.05$.

The S1P effects on the rat cardiovascular system are described in Sugiyama, A., N.N. Aye, Y. Yatomi, Y. Ozaki, K. Hashimoto 2000 Effects of Sphingosine-1-Phosphate, a naturally occurring biologically active lysophospholipid, on the rat cardiovascular system. Jpn. J. Pharmacol. 82: 338-342, hereby incorporated by reference in its entirety.

Measurement of Mouse Acute Toxicity

A single mouse is dosed intravenously (tail vein) with 0.1 mL of test compound dissolved in a non-toxic vehicle and is observed for signs of toxicity. Severe signs may include death, seizure, paralysis or unconciousness. Milder signs are also noted and may include ataxia, labored breathing, ruffling or reduced activity relative to normal. Upon noting signs, the dosing solution is diluted in the same vehicle. The diluted dose is administered in the same fashion to a second mouse and is likewise observed for signs. The process is repeated until a dose is reached that produces no signs. This is considered the estimated no-effect level. An additional mouse is dosed at this level to confirm the absence of signs.

Assessment of Lymphopenia

Compounds are administered as described in Measurement of Mouse Acute Toxicity and lymphopenia is assessed in mice at three hours post dose as follows. After rendering a mouse unconscious by CO_2 to effect, the chest is opened,

0.5 mL of blood is withdrawn via direct cardiac puncture, blood is immediately stabilized with EDTA and hematology is evaluated using a clinical hematology autoanalyzer calibrated for performing murine differential counts (H2000, CARESIDE, Culver City CA). Reduction in lymphocytes by test treatment is established by comparison of hematological parameters of three mice versus three vehicle treated mice. The dose used for this evaluation is determined by tolerability using a modification of the dilution method above. For this purpose, no-effect is desirable, mild effects are acceptable and severely toxic doses are serially diluted to levels that produce only mild effects.